The Journal of
NERVOUS and MENTAL DISEASE

VOL. 128, NO. 4
April, 1959
SERIAL NO. 917

NEUROPATHOLOGIC, CLINICAL, ETIO-PATHOGENETIC AND THERAPEUTIC CONSIDERATIONS IN MULTIPLE SCLEROSIS

ARMANDO FERRARO, M.D.[1]

The ever-lasting interest in the problem of multiple sclerosis has been enhanced by recent investigations on the clinical pathological and etio-pathogenetic aspects of acute disseminated encephalomyelitides in humans, and of experimentally induced "allergic encephalomyelitis" in animals.

A first important problem which developed from these investigations relates to the similarities or even identity between the experimentally induced encephalomyelitides, and the human active disseminated encephalomyelitides and multiple sclerosis.

It had been established ever since the original contribution by Rivers Schwentker (38) and co-workers that injections of suspensions of normal brain tissue, homologous or heterologous, intramuscularly in monkeys will determine an involvement of the central nervous tissue, which from the clinical and pathological standpoint, had been classified as an "acute disseminated encephalomyelitis." The first confirmation of such findings was presented in 1940 by Ferraro and Jervis (14) who also felt that the encephalomyelitis in question was to be considered as an allergic reaction of the central nervous tissue, to specific anti-brain antibodies originating from the intramuscular injection of normal brain tissue.

In order to produce that encephalomyelitis a large number of injections were necessary. It took Ferraro and Jervis a minimum of 29 injections to a maximum of 103 in the course of 112 to 405 days to determine involvement of the central nervous system.

A few years later, Freund (18) and his co-workers devised a new method of preparing the brain tissue for intramuscular injections in order to enhance the production of anti-brain antibodies, and therefore accelerate the tempo of production of the allergic encephalomyelitis. They resorted to emulsions of brain tissue in association with so-called adjuvants: killed tubercle bacilli, paraffin oil and Falba. With their technique they were able to produce in animals the same encephalomyelitic process within the period of only two to three weeks. Confirmatory results were soon published by Morgan (34) and by Kabat, Wolf and Bezer (23). This new procedure gave the origin to numerous investigations including the additional one by Ferraro and Cazzullo (11) and lent itself to the accumulation of new and interesting data on the pathology and immunological aspects of this experimental disease.

The consensus of opinion concerning the etio-pathogenesis and pathology of this experimental disease was of a two-fold nature. 1) The disease was considered as being related presumably to an allergic process. 2) The pathology of the disease was considered as an inflammatory one and characterized by perivascular reaction of polymorphonuclear cells in the very acute stages, lymphocytes later on, and marked proliterative reaction of the microglia cells.

[1] 150 East 93rd Street, New York City. Formerly Clinical Professor of Psychiatry, Columbia University; Formerly Principal Research Scientist, New York State Psychiatric Institute, New York.

Furthermore, perivascular demyelination was the outstanding characteristic of the acute stages followed in the sub-acute and chronic stages by astroglia reaction and formation of glia scars (11).

In view of the close similarities between the pathological findings in this experimental disease and the same findings in human cases of other important primary demyelinating diseases, the writer advanced the concept that the pathology of human demyelinating diseases could be considered as expression of an allergic reaction of the central nervous system to antigens, the source of which was to be investigated by future research. This concept was advanced in 1944 (10) also on the basis of experimental work on anaphylaxis of the brain which the Kopeloffs carried on using monkeys, and the pathology of which was investigated by Jervis and myself (22).

The similarities between the pathologic process of the experimental allergic encephalomyelitis and the human demyelinating diseases extended, in my opinion, to the acute disseminated encephalomyelitides which follow infectious or exanthematic diseases of children and adults, to the so-called acute multiple sclerosis, and to the acute encephalomyelitides which follow vaccination against small-pox and rabies.

Presently this concept of similarities—and even identity—of the pathologic process in the central nervous system of all the above-mentioned clinical conditions, has been accepted by most investigators with the reservation that such an identity of pathological reaction and etio-pathogenesis must remain limited to the group of the acute disseminated encephalomyelitides following infectious or exanthematic diseases, and to the group of the encephalomyelitides following vaccination against small-pox or rabies. Acute multiple sclerosis or chronic multiple sclerosis, according to most investigators, constitute separate entities, the etio-pathogenesis, the clinical course and the pathology of which should not be confused with the acute disseminated encephalomyelitides mentioned above (5, 20, 37).

It is obvious that if the unitarian concept of all these demyelinating conditions will eventually prove to be correct, considerable progress will have been made in the understanding of human multiple sclerosis, inasmuch as an immuno-biologic approach to the pathogenesis and possibly treatment of multiple sclerosis could be envisaged.

Which are the bases on which rest my concept of the identity of the pathological, clinical and etio-pathogenetic aspects of multiple sclerosis and the already mentioned encephalomyelitides?

In discussing each of these aspects it must be realized that a consideration of minute details would entail considerations of technical nature involving more than a working knowledge of neuropathology, immunochemistry and virology. I will therefore limit what follows to a number of general considerations which, it is hoped, will be sufficient to clarify my ideas in the eyes of the clinical neurologists entrusted with the diagnostic and therapeutic management of human multiple sclerosis.

NEUROPATHOLOGICAL ASPECTS

In acute disseminated encephalomyelitides following general infectious diseases, or developing in the course or following exanthematic diseases of childhood (measles, varicella, scarlet fever, etc.), or developing in the course or following vaccination against rabies or small-pox, as well as in the so-called acute multiple sclerosis, the following main histo-pathologic features of the central nervous system are encountered: inflammatory reaction, demyelination, involvement of axiscylinder, glia reaction and occasional necrosis and hemorrhages.

Inflammatory reaction: In all cases, the blood vessels—especially the veins—are surrounded by a cuffing of inflammatory cells which in the very acute and severe

cases are constituted mainly by polymorphonuclear cells. In the lesser acute cases, the lymphocytes predominate. However, in all acute cases plasmacells are present in variable number.

Demyelination: In all cases, the demyelination is an outstanding histopathologic feature. The demyelination predilects the perivascular areas and reaches various degrees of intensity, from pallor of myelin sheaths to complete destruction of these sheaths. The demyelination, though generally related to a centrally located blood vessel, may be encountered apparently free from such a topographical relationship.

Involvement of Axis-cylinders: Axis-cylinders may be involved by the pathological process and various degrees of swelling and disintegration of nerve-fibers are often encountered. Corresponding, however, to areas of lesser myelin involvement, the axis-cylinder are better preserved and even intact.

Glia reaction: In the early acute stages of the pathologic process, the reaction of the glia cells seem to predilect the so-called microglia cells which undergo, particularly in the perivascular areas of demyelination, various stages of transformation into compound granular corpuscles. These compound granular corpuscles contribute to the formation of the perivascular cuffing. The oligodendroglia cells, in a minor measure, also contribute to the formation of compound granular corpuscles, and thus explain to a certain degree that corresponding to the areas of demyelination there is a diminution or even a disappearance of these cells. However, in certain areas, the number of oligodendroglia cells still present without having undergone marked pathological changes, is considerable.

In the chronic stages of the pathologic process, the astrocytes react through hypertrophy and hyperplasia and through the formation of increased number of glia fibrils, thus contributing to the formation of scattered glia scars. Evidently such glia scars are lacking in cases of acute disseminated encephalomyelitides lasting a few days or a few weeks.

Necrotic and hemorrhagic areas: Occasionally one finds small areas of necrosis here and there in the gray matter or in the white matter, and particularly in the periventricular areas. The occurrence of scattered areas of necrosis does not certainly justify the designation of the process as a necrotizing process, as indicated by Hallevorden (20) in his description of the experimental allergic encephalomyelitis. The same applies to the occasional occurrence of small hemorrhagic areas which may be detected in some cases of experimentally induced encephalomyelitis, or encephalomyelitis following exanthematic diseases or even cases of acute multiple sclerosis.

All these pathologic changes occur not only in human cases of acute disseminated encephalomyelitides and acute multiple sclerosis, but also in cases of reacutization or relapses in the clinical course of chronic multiple sclerosis. In such cases, these characteristic features are seen to develop generally at the periphery of an old cicatricial plaque of gliosis or in areas not previously affected by the disease.

Distribution of the pathologic lesions: In all of the above-mentioned clinical and experimental instances, the pathologic process may at times be very symmetrical particularly in the spinal cord. Furthermore, the pathologic process in these instances of human or animal material has a tendency to coalescence, as a result of which small plaques of perivascular distribution may ultimately give origin to larger areas of demyelination, the relationship of which to blood vessels may be lost in the process of confluence (15). These findings do not vary from the ones often reported in chronic multiple sclerosis.

Of considerable interest is the fact that from a neuro-pathologic standpoint, the investigators who deny identity between acute encephalomyelitides and acute or

chronic multiple sclerosis, accept the identity between experimentally induced allergic encephalomyelitis, the acute infectious and post-exanthematic encephalomyelitides and the encephalomyelitides developing in the course of vaccination against small-pox or rabies. However, when confronted in human cases with the pathology of encephalomyelitis following antirabies vaccination, in which the features are strikingly identical with the pathology of human multiple sclerosis (48) they resort to the rather simplistic explanation that in these cases the pathology might be the expression of multiple sclerosis which has developed concomitantly but independently, in the course of the vaccination (50).

Finally a last consideration from the histopathologic standpoint is the one that has been advanced by the advocates of the dualistic conception (31, 51). Investigators maintaining this position hold that in multiple sclerosis the involvement of the myelin sheaths precedes the appearance of inflammatory reaction and that the primary process is therefore a myelinolitic process. In my opinion, the argument appears somewhat captious because of the fact that, far away from the areas of perivascular demyelination, one finds areas of light involvement of the myelin sheaths both in human cases of multiple sclerosis and in cases of experimental allergic encephalomyelitis. In both situations the possibility exists that primary involvement of the myelin sheaths may be essential to the formation of a complete encephalitogenic antigen, and in both cases the involvement of the myelin sheaths by various etiological agents might constitute the primary histochemical step in triggering off the allergic reaction and its inflammatory component. It would make no difference which etiologic agent may be at work. It may be a virus, it may be a bacterial toxine, it may be an enzyme (31). The important point, as will be discussed later, is that it takes a combination of at least two factors to create the demyelinating antigen. The chronology of the pathology, affecting first the myelin sheath becomes unimportant, and cannot be used in creating a different etio-pathogenesis for multiple sclerosis and for other acute disseminated demyelinating encephalomyelitides.

CLINICAL ASPECTS

Is there any available set of pathognomonic symptoms by which clinicians can establish a sure diagnosis of multiple sclerosis, and differentiate the disease from acute disseminated encephalomyelitides in humans, and from the experimental allergic encephalomyelitis in monkeys? If one were to consider the symptomatology of the so-called classical type of human chronic progressive multiple sclerosis, one could be inclined to answer in the affirmative. But if one extends the clinical concept of multiple sclerosis to the acute forms, as it should be extended, the monosymptomatic, the oligosymptomatic, the abortive and the stationary forms, the resources and the ingenuity of the clinician are evidently severely challenged.

In the acute stage of multiple sclerosis is there any clinical characteristic which may indicate with certainty its subsequent development into the chronic stage? And is there any sure way to differentiate the symptoms of acute multiple sclerosis from those of acute disseminated encephalomyelitides in human, or of experimental allergic encephalomyelitis in monkeys? The answer appears to be "no."

The difficulty—if not the impossibility at times—in differentiating an acute incipient multiple sclerosis from the various types of acute disseminated encephalomyelitides in humans is supported by important clinical elements:

Elements based on clinical varieties: In all these acute conditions, the same clinical varieties have been described ever since the time of Charcot, Marie and Oppenheimer to the very recent report of McAlpine, Compston and Lumsden (30): The most outstand-

ing clinical varieties are a) the spinal type, b) the cerebral type, and c) the cerebrospinal type.

The occurrence of abortive forms "formes frustes" has also been recognized in both acute encephalomyelitides as well as in multiple sclerosis. Ever since Charcot's description of "formes frustes" in multiple sclerosis, in which one symptom only may be present in isolated form or predominate over the others, this concept of monosymptomatic forms of multiple sclerosis has been accepted by clinicians who consider unilateral retro-bulbar neuritis, for instance, to be the initial or the sole symptom of multiple sclerosis. This acceptance varies from a figure of 14 per cent in the 38 cases of Adams and Sutherland (1) to 20 per cent in the 793 cases of Muller (35) and to 27 per cent in the 666 cases of McAlpine, Compston and Lumsden (30). The unilateral retrobulbar neuritis which the latter authors diagnose as multiple sclerosis may be followed by a more or less rapid recovery. At other times, either soon after the optic neuritis, or 15 to 39 years following recovery from the optic symptoms, additional symptoms of multiple sclerosis develop. Hyllestedt (21) reported that out of 52 patients who originally developed unilateral retrobulbar neuritis (therefore multiple sclerosis, according to McAlpine *et al.*), seven later developed additional symptoms of multiple sclerosis, 12 disclosed minimal symptoms of multiple sclerosis while 33 (60 per cent) had remained well, when all these patients were re-examined 20 years later. On the other hand encephalomyetides of the acute type following undetermined infectious diseases, or following exanthematic infectious diseases, are also known to follow an acute course manifesting only a few neurological symptoms and leading to recovery.

Elements related to the onset of the disease: The onset of the disease in both multiple sclerosis and acute disseminated encephalomyelitides seems also to run a parallel course. We are all familiar with the acute, subacute or almost fulminating type of onset in acute disseminated encephalomyelitides, but less known is the fact that the same type of onset may occur in cases ultimately diagnosed as multiple sclerosis. Among 219 cases of multiple sclerosis reported by McAlpine *et al.*, 38 (17.3 per cent) developed the disease fully within a matter of minutes; 64 (29.2 per cent) within one day to one week; and 31 (14.2 per cent) within one to under eight weeks.

Elements related to symptomatology: Early neurological signs, including diffuse involvement of the central nervous system, drowsiness, meningeal signs, neuritic pains and fever, disclose no clear-cut distinction in favor of one or the other condition. The same applies to other clinical symptoms developing in the course of the disease.

Elements related to remissions and relapses: In the past, hopes for a differential diagnosis between acute disseminated encephalomyelitis and multiple sclerosis centered around the occurrence of remissions and relapses, which were considered characteristic for multiple sclerosis. However, while McAlpine *et al.* and Muller reported only 10 per cent of their cases of multiple sclerosis showing lack of remissions and following an uninterrupted chronic progressive course, Brown and Putnam (6) reported 41 out of 133 cases of multiple sclerosis which never disclosed remissions and Thygessen (45) reported that 40 per cent of his cases of multiple sclerosis failed to show any remissions. Birley, Oxon and Dudgeon (2) must have been so impressed by the variability of remissions in multiple sclerosis that they recognized two clinical types of this disease: a) the remitting type and b) the chronic progressive type without remissions.

On the other hand, remissions and relapses in the course of acute disseminated encephalomyelitis have been reported more and more frequently. In 1933, Stout and Karnosh (44) stated that, "evidence is ac-

cumulating to show that the occurrence of remissions and relapses does not exclude the diagnosis of encephalomyelitis." Miller and Evans (33), in reporting on the follow-up of 34 cases of acute disseminated encephalomyelitis, include two cases of the cerebral type and one case of visual failure in all of which the diagnosis of acute disseminated encephalomyelitis was made and sustained in spite of remissions and relapses which occurred in a variable course of time up to 15 years after the onset of the initial episode. McAlpine (28) in 1931 described four cases which he diagnosed as "spontaneous acute encephalomyelitides." In 1946 (29) he again reported on two of these cases and on a third case which he had examined later in 1931. Each of these three cases had, since 1931, relapsed on more than one occasion, one of them terminating fatally in 1941. Remissions and relapses did not prompt McAlpine to change his original diagnosis of acute disseminated encephalomyelitides.

Does a stationary clinical course of the disease favor one or the other diagnosis? It does not seem so, inasmuch as cases of both multiple sclerosis and disseminated encephalomyelitides have been reported in terms of stationary symptomatology. A case of acute disseminated encephalomyelitis, for instance, was summarized by Miller and Evans (33) as a stationary type of encephalomyelitis as follows. "Acute disseminated encephalomyelitis with loss of consciousness and lymphocytosis in the cerebrospinal fluid, leaving ten years later a disabling, non-progressive and non-recurrent neurological syndrome consisting of dysarthria, ataxia, diplopia, nystagmus and tremors."

The lack of decisive clinical criteria to establish a differential diagnosis between the acute stage of multiple sclerosis and acute disseminated encephalomyelitis is reflected in the fact that not infrequently an original diagnosis of acute encephalomyelitis had to be changed years later into one of multiple sclerosis. Thygessen (46), reporting on 24 survivors out of 29 cases originally diagnosed as acute disseminated encephalomyelitis and re-examined eight to 15 years later, found that in seven of them (34 per cent) the diagnosis had to be changed to that of multiple sclerosis. In two other, fresh myelitic changes were found in the spinal cord. In 1950 Van Bogaert (4) reported the follow-up study of 19 cases of acute disseminated encephalomyelitis diagnosed as such between 1927 and 1932. Of these cases four developed typical multiple sclerosis and one disclosed at autopsy a pathology closely resembling multiple sclerosis (case of Van Bogaert and Dagnelie), a total of 26 per cent of his 19 cases.

In my opinion it follows that multiple sclerosis in its acute stage can be considered as an acute "disseminated demyelinating encephalomyelitis," the etio-pathogenesis of which is as unknown to us as the etio-pathogenesis of other cases of acute disseminated encephalomyelitides. Its advanced stage, chronic multiple sclerosis, could be designated as "chronic disseminated encephalomyelitis." This designation of chronic disseminated encephalomyelitis for the chronic variety of multiple sclerosis, is in my opinion a better and more appropriate designation for the disease, and more in harmony with our present day knowledge of its clinico-pathologic evolution and of its presumable toxic allergic or infectious-allergic etio-pathogenesis. The simple designation of "multiple sclerosis" for such a polymorphous disease is evidently inappropriate, inasmuch as the term designates *a complex disease* only by the *final stage of a complex pathologic process.*

ETIO-PATHOGENETIC ASPECTS

In stating the concept that multiple sclerosis in its advanced stages must be considered as the chronic aspect of the same etio-pathogenetic process responsible for the acute disseminated encephalomyeli-

tides, I have used the terms "infectious-allergic" or "toxic allergic." This terminology implies that I consider the concomitant action of at least two elements at the base of the etio-pathogenic mechanism: 1) the allergic (the antigen element) and 2) the infectious or toxic element.

For several years we qualified as allergic the nature of the experimentally induced encephalomyelitis following intramuscular injections of nervous tissue in animals. Immunologically the appearance of anti-brain antibodies reported by various investigators was mainly responsible for that designation.

The concept that the nature of the pathologic process in experimentally induced encephalomyelitis is the same in the acute demyelinating encephalomyelitides in humans, presumably of allergic nature, seems to have been generally accepted, and investigators have been busy in the search for the antigen fraction of the nervous system responsible for the experimental disease. It is supposed to be a proteo-lipid according to Folch (17) and his collaborators, or a collagen-like substance according to Kies, Alvord and Roboz (24) present in the injected nervous tissue.

Where, however, are partial antigens to be found in the human body? First, they also may be liberated from the central nervous system itself in the course of various neurotropic toxic or infectious processes primarily involving the nervous system or following a primary infection of some other organ or organ system. Partial antigens of an identical chemical nature of the nervous antigens, may be also liberated in various other organs or tissues, in the course of focal or general extra-neural diseases (skin, lungs, testis, placenta, etc.). In the gastro-intestinal system partial antigens may be liberated by products of our daily diet; fish, eggs, meat, milk, etc. in the course of our intermediary metabolism.

Is a partial antigen, even if chemically identified, sufficient *per se* to determine a demyelinating encephalomyelitis? It is my contention that a partial antigen needs the interaction of an additional element in order to become a complete and total antigen, capable of determining the demyelinating encephalomyelitis. This additional element must be looked for in concomitant infectious agents or toxines, thus clarifying the designation of "infectious-allergic" or "toxic allergic" which I have used.

It is true that in 1940, in collaboration with Dr. Jervis (14), I was able to induce in monkeys a demyelinating encephalomyelitis with the use of simple aqueous brain solution or alcholic brain extracts. However, in the light of the large number of injections to which we resorted in order to induce the disease (a minimum of 29 injections to a maximum of 103, in the course of 112 to 405 days), I recently have been considering in retrospect the fact that in those early experiments we paid little attention to the swelling, calor and rubor of the areas repeatedly injected. I can now assume that in these traumatized areas, various types of chemical or even infectious inflammatory reactions may have occurred, leading to the formation of a complete encephalitogenic antigen, through the combination of the aqueous or alcholic brain extract, acting as a hapten, with one or more local toxic or infectious products.

This interpretation is supported by the well known findings of Freund (18) and his collaborators, that the addition of adjuvants, particularly killed tubercle bacilli, in the brain emulsion, elicits the encephalomyelitis within three weeks, as compared to the many months required in our original experiments.

Furthermore, if partial antigens resulting from disintegration of nervous tissue, could *per se* determine primary or extensive demyelinating encephalomyelitides, one would find such a complication in many more pathological processes involving the central nervous system (vascular, degen-

erative, neoplastic, etc.), an occurrence hardly ever reported.

If infectious agents, viruses or bacteria, are essential to the development of demyelinating encephalomyelitides of the acute or of the chronic type; do we find, in the clinical data related to acute and chronic multiple sclerosis in humans, any indication of such an intervention? The answer is in the affirmative on several counts. 1) Occurrence of acute disseminated encephalomyelitides, later diagnosed multiple sclerosis, following infectious diseases local or general. 2) Occurrence of infectious conditions which at times precede the onset of a clinical picture that follows a chronic progressive course diagnosed as multiple sclerosis. 3) Regressions of clinical symptoms of multiple sclerosis coinciding with subsidence of infections, as determined serologically (43) and occurrence of relapses following intercurrent infectious processes. 4) Reports of acute hemorrhagic encephalitides, closely related to allergic encephalomyelitides, following general infectious processes or even exanthematic diseases (26).

The fact that infectious agents, viral or bacterial, seem to contribute to the development of acute or chronic demyelinating encephalomyelitides, does not imply a pure and simple infectious etio-pathogenesis of multiple sclerosis. Infectious agents are involved inasmuch as they themselves represent substances of the adjuvant type, which in combination with released partial antigens will create a complete encephalitogenic one.

The search for an infectious agent responsible *per se* for acute demyelinating encephalomyelitides or multiple sclerosis dates back to several decades. Reports have been published now and then on the isolation of bacterial viruses or even spirochetes which have been considered the primary etiologic agent of the disease (32, 40, 47). Never have such reports been substantially confirmed, nor have other investigators been able to reproduce the disease experimentally.

The reason for this failure lies, in my opinion, in the fact that these investigators have considered the infectious agent which they isolated as the sole factor responsible for the disease. The search for one single specific infectious agent cannot be the answer to the etio-pathogenesis of multiple sclerosis. This is why I cannot rally myself to the opinion recently expressed by Sabin (39) that the virus of herpes simplex may be the specific or primary virus responsible for multiple sclerosis. This virus is supposed primarily to affect the oligodendroglia cells, which some investigators consider the primary site of the pathologic process of multiple sclerosis, in relation to disturbed production or preservation of the myelin tissue (19, 27).

One has to think only of the fact that following infections due to entirely different etiological agents (streptococci of scarlet fever, viruses of influenza, measles, varicella, variola, rabies, vaccinia, etc.) the same type of acute disseminated demyelinating encephalomyelitides may develop. In addition, the process of demyelination in human multiple sclerosis can hardly be differentiated from the process of demyelination in encephalomyelitis following vaccination against rabies in humans. No virus of herpes simplex seems involved in all these cases.

Furthermore, in the cases of neurotropic viruses infections, the brain pathology is quite typical, as for instance in poliomyelitis and epidemic encephalitis or other viral infections where demyelination is far from being the outstanding feature of the neuropathologic process.

However, a virus infection, which usually determines a typical viral encephalitis with predominant involvement of nerve cells, and often disclosing intracellular inclusions, may at times determine diffuse demyelination. This is the case of the so-called "inclusion

encephalitis" first described by Dawson and later on described by Pette and Doering as "nodular encephalitis." That same virus of the inclusion encephalitis may under special circumstances produce a disease described by Van Bogaert (3) under the name of "subacute sclerosing encephalitis" in which demyelination of extensive distribution has been occasionally reported.

This is also the case of the virus of rabies which under usual circumstances determines an encephalitis characterized by specific inclusions (Negri bodies). However, that same virus, in combination with nervous tissue in the anti-rabies vaccine, may determine an acute or subacute demyelinating encephalomyelitis, the pathologic characteristic of which cannot be differentiated from the pathology of multiple sclerosis (48).

In animal pathology, we also find an outstanding example of a viral infection which determines the well known "canine encephalitis" possessing typical histopathological features. Yet under certain circumstances the same virus may determine various degrees of demyelination (25, 47) which in some cases is so severe and diffuse as to have been labeled "acute multiple sclerosis" by Scherer and Collet (41).

Why is it than an infectious agent capable *per se* of determining only a characteristic "viral encephalitis", will under certain circumstances determine an acute demyelinating encephalomyelitis? We cannot escape the speculation that in order to determine a demyelinating encephalomyelitis, an infectious agent needs the presence of an "additional concomitant factor" which in combination with it will give origin to a final product capable to induce the demyelinating disease.

In support of that speculation, we must also remember the fact that in animal experimentation one of the essential factors in determining the allergic encephalomyelitis is the brain tissue injected intramuscularly and containing the necessary antigen responsible for the formation of the anti-brain antibodies. On the other hand, in Freund's emulsion, the presence of killed tubercle bacilli is of paramount importance. Here is a typical example of a partial antigen (fractions of the brain tissue) in combination with the chemical substances of the killed bacilli, a combination which presumably generates the complete encephalitogenic antigen responsible for the allergic encephalomyelitis.

The speculation is therefore justified that when an infection, viral or bacterial, results in a demyelinating disease of the nervous system, it is because the infectious agent has combined itself with a partial antigen and has thus formed a complete antigen capable to produce the specific anti-brain antibodies.

What I have said about the infectious agents *per se* may be applied to bacterial eso- or endotoxines, viral toxines or other toxines having the attributes of proteins.

These views, presented at the IIIrd International Congress of Neuropathology (Brussels, July 1957) seem to have received indirect confirmation from the findings of Colover (8), who succeeded in determining a demyelinating encephalomyelitis in guinea pigs via injection of a combination of chemically purified tubercle bacilli fractions (chemically composed of about 70 per cent of proteins or peptides, 12 per cent of polysaccharide and about 10 per cent of mycolic acid) with the collagen-like fraction (Roboz) extracted from nervous tissue. Such a combination, considered even at a chemical level, seems therefore essential for the formation of a total demyelinating antigen.

THERAPEUTIC CONSIDERATIONS

It is not my intention to discuss the therapeutic management of the advanced cases of multiple sclerosis with all its implications of physical therapy and re-educational activities. Nor will I delve in the already established general medical approach to the

treatment of acute cases of encephalomyelitides or multiple sclerosis. It goes without saying that because of the suspicion that infectious agents play a part in the precipitation of the first clinical development of symptoms or in triggering off clinical relapses, a particular attention should be given to the elimination of all sorts of suspected foci of "focal infections" in the respiratory tract, gastro-intestinal tract, and uro-genital system or to the presence of possible atypical tubercular infection, etc. All these aspects as well as the attempt at favorably influencing the course of the disease via appropriate antibiotics or corticoid preparations presumably beneficial in counteracting the inflammatory process are already well taken care of by clinical neurologists.

The new therapeutic point which I am interested in developing, is the one, as yet unexplored, of the bio-immunological approach. This concept which I am presenting for investigation in human cases of acute encephalomyelitides and acute multiple sclerosis, is based on animal experimentation which I carried out for the first time in 1949 in collaboration first with Dr. Cazzullo and then with both Drs. Cazzullo and Roizin (12, 13, 16).

In view of the fact that in experimental allergic encephalomyelitis the presence of antibrain-antibodies circulating in the blood had been well established (thus substantiating the concept of a presumably allergic origin of the encephalomyelitis), I considered the possibility of preventing the development of the encephalomyelitis by desensitizing guinea pigs through repeated intramuscular injections of brain tissue in emulsion or aqueous solution. This procedure, commonly applied in other immunological therapies, gave us favorable results in this original attempt at prevention of the allergic encephalomyelitis in animals.

In the preliminary experiment, we used 12 guinea pigs which were prepared with intramuscular injections of one c.c. of brain emulsion every other day, and received altogether 15 injections within a month. Four days after the last preparatory injection, the animals received an intraperitoneal injection of the "disease-producing emulsion" (Freund's emulsion). As a control, we used 13 guinea pigs which were not given desensitizing doses of brain emulsion prior to the injection of the disease-producing emulsion.

The control group gave the following results. Twelve animals disclosed the first symptoms of motor weakness from six to 14 days following the disease-producing injection. Of these, nine died within two to eight days following the appearance of the first symptoms. One died 33 days after the injection, and one was killed in extremis 51 days after the injection. Two animals survived for over five months but disclosed moderate neurological symptoms related to the encephalomyelitis.

The protected group yielded the following results. One animal died from bronchopneumonia 40 days after the injection of the disease-producing emulsion, without having disclosed neurological symptoms. A second animal died suddenly two months after the injection, without disclosing neurological symptoms. A third animal developed the first symptoms of encephalomyelitis three weeks after the injection and was still completely paralyzed 147 days after the onset of the paralysis. The remaining *nine* animals were alive and in good health approximately five and a half months after the injection of the emulsion-producing disease. All but two of them had also recovered from a mild hypotonia of the hind legs which was present in some of them, following the injection of the disease-producing emulsion.

Such favorable results in our preliminary investigation were indeed very encouraging. The explanation of the favorable results was a difficult one and was left for future investigations. We did speculate, however, on the possibility that in the course of re-

peated intramuscular injections of normal brain tissue, there occurred a production of anti-brain antibodies in sufficient amount to neutralize the antigen present in the emulsion of the disease-producing combination. Against this interpretation was, however, the fact that normal brain tissue *per se*, is a poor generator of antibodies. The future investigation of the mechanisms at work in this type of experiment was left in abeyance, pending collaboration with a competent immunologist, but not before we repeated a second experiment which gave us approximately the same favorable results.

This approach to the prevention of experimentally induced encephalomyelitis was not explored by other investigators for some years. However, in 1957 three separate groups of investigators began working in this area, using repeated injections of brain tissue in both new-born and adult animals. Preliminary results confirming our original data were presented at a symposium on experimental allergic encephalomyelitis at the National Institute of Health in October 1957 by Paterson (36) and by Condie (9). Paterson related his favorable results in the prevention of the disease to what he termed "tolerance" of the organism to products of the injected tissue. More recently, Waksman (49) of Boston, in a paper to be published in the July 1959 issue of the Journal of Neuropathology, will bring additional confirmatory data to this very important problem of prevention and will discuss his favorable results in the light of immunological theories.

At the present, there is therefore enough evidence in experimental work to justify further investigations along immuno-biological lines with the view to ascertaining if a process of "desensitization" or "tolerance" (Paterson's term) could not be applied in humans in order to prevent the occurrence of acute allergic encephalomyelitis or its development into a chronic stage. This immunological approach, stemming from our preliminary investigations in 1949, constitutes in my opinion a ray of hope in the very important problem of therapy for demyelinating diseases, a problem which thus far has remained an unanswered challenge.

The "desensitizing" method, if one wishes to apply such a term to our early procedure, is not the only one which should be investigated in any effort to tackle the problem of therapy of the demyelinating diseases from an immuno-biological standpoint. In connection with the 1949 investigations described above, I proposed and carried out a second procedure; the intramuscular injection in the animals of a relatively "massive" but single dose of normal brain tissue prior to the injection of the emulsion-producing disease. My notion was to create a kind of intramuscular "substitute brain" which could attract towards it the anti-brain antibodies which would result from the injection of the emulsion-producing disease (brain tissue and Freund's adjuvants). This phenomenon, which I termed "deflection," would represent a detour or "short-circuit" for the anti-brain antibodies which would find it easier to reach the "substitute" or "accessory" brain rather than the animal's brain proper, protected by the brain-blood barrier.

Fifteen guinea pigs were used in this experiment. All the animals were given a single intramuscular injection of 400 milligrams of normal brain in emulsion. A few minutes after this "protective" injection, the animals were injected intraperitoneally with one c.c. of the emulsion-producing disease. As a control group, we used 15 guinea pigs which were injected solely with the disease-producing emulsion.

The results were as follows. Of the 15 animals given the injection of normal brain tissue, five developed symptoms of various degree of an allergic encephalomyelitis and died within a period of a few weeks to over three months. Of the remaining ten animals, one was still paralyzed after several months and nine were still alive and in good health. These results are in significant contrast to

the results obtained with the control group, which did not receive the protective normal brain tissue injection. Twelve of the control group animals died within a period of from 15 to 39 days following the injection of the emulsion-producing disease, disclosing accentuation of the motor weakness and the paraplegia or tetraplegia characteristic of the encephalomyelitis. Of the remaining three still alive after several months, two presented respectively motor weakness and paresis of the hind legs. Only one animal remained alive and healthy, compared with nine alive and healthy in the experimentally protected group.

All these data seem to point to the possibility that an equivalent technique could be applied to human cases of demyelinating diseases in order to prevent or modify the course of the acute disseminated encephalomyelitides. The problem of "prevention" will of necessity be approached from the standpoint of desensitizing human beings against the pathologic effects of the allergen. The problem of "modifying favorably" the course of an acute disseminated encephalomyelitis may have to be approached through the injection of a single dose of antigen ("deflection" method), sufficient to create a so-called accessory brain, so that the anti-brain antibodies, once formed, may find their way possibly toward the injected brain and thus spare from further damage the central nervous system of the patient.

In my estimation, the field is open for intense investigations of the therapeutic approach of human demyelinating diseases via immuno-biologic methods which up to the present time has remained unexplored.

In view of the progress made in isolating fractions of the central nervous system (proteo-lipids or collagen-like substances) responsible for the antigenic properties of the central nervous system, a further step in the animal experimentation or in investigations in humans would be the use of the above fractions rather than the use of the whole brain, in future attempts at preventing or modifying the course of demyelinating diseases.

The important question as to the possible deleterious effect of intramuscular injections of brain tissue or of its fractions has already been answered by investigations of Cerletti (7) who has resorted to this type of injection in order to modify the clinical course of mental diseases. No ill effect seem to have been observed by this author in his investigations. Following his preliminary report, in collaboration with Roizin, at the New York State Psychiatric Institute, we have treated twenty schizophrenic patients with repeated injections of suspension of nervous tissue (daily injections for 20 days), without apparent harmful effect, except for the occurrence in one case of an epileptic seizure in a patient who already was suffering from epilepsy. Because of the negative results in modifying the course of the mental illness in our patients, the data of this investigation were not published.

It is hoped that what has been reported here will stimulate investigations in this area, to open a new and broader approach to the study of the etio-pathogenesis and treatment of human demyelinating diseases.

REFERENCES

1. Adams, D. K., Sutherland, J. M. and Fletcher, W. B. Early clinical manifestations of disseminated sclerosis. Brit. M. J., **2**: 431–436, 1950.
2. Birley, J. L., Oxon, M. D. and Dudgeon, L. S. A clinical and experimental contribution to the pathogenesis of disseminated sclerosis. Brain, **44**: 150–222, 1921.
3. Bogaert, L. van Une leuco-encéphalite sclérosante subaigue. J. Neurol. Neurosurg. & Psychiat., **8**: 101–120, 1945.
4. Bogaert, L. van Post-infectious encephalomyelitis and multiple sclerosis. J. Neuropath. & Exper. Neurol., **9**: 219–249, 1950.
5. Bogaert, L. van Sur les maladies démyélinisantes. Acta neurol. et psychiat. belg., **54**: 692–715, 1954.
6. Brown, M. R. and Putnam, T. J. Remissions in multiple sclerosis. Arch. Neurol. & Psychiat., **41**: 913–920, 1939.
7. Cerletti, U. Sostanze di estrema difesa prodotte dall'electroshock (Acroagonine). Lav. Neuropsichiat., **1**: 367, 1947.
8. Colover, J. Experimental allergic encephalo-

myelitis and its immunochemistry. Proc. Roy. Soc. Med., **51**: 745–747, 1958.

9. Condie, R. M., Kelly, J. T., Campbell, B. and Good, R. A. Prevention of experimental allergic encephalomyelitis by prior injections of homologous spinal cord. Fed. Proc., **16**: 24, 1957.
10. Ferraro, A. Pathology of demyelinating diseases as an allergic reaction of the brain. Arch. Neurol. & Psychiat., **52**: 443–483, 1944.
11. Ferraro, A. and Cazzullo, C. L. Chronic experimental allergic encephalomyelitis in monkeys. J. Neuropath. & Exper. Neurol., **7**: 235–260, 1948.
12. Ferraro, A. and Cazzullo, C. L. Prevention of experimental allergic encephalomyelitis in guinea pigs; preliminary report. J. Neuropath. & Exper. Neurol., **8**: 61–69, 1949.
13. Ferraro, A. and Cazzullo, C. L. Prevention of experimental allergic encephalomyelitis in guinea pigs. J. Neuropathol. & Exper. Neurol., **8**: 226–231, 1949.
14. Ferraro, A. and Jervis, G. Experimental disseminated encephalopathy in the monkey. Arch. Neurol. & Psychiat., **43**: 195–209, 1940.
15. Ferraro, A. and Roizin, L. Neuropathologic variations in experimental allergic encephalomyelitis. J. Neuropath. & Exper. Neurol., **13**: 60–89, 1954.
16. Ferraro, A., Roizin, L. and Cazzullo, C. L. Experimental studies in allergic encephalomyelitis; prevention and production. J. Neuropath. & Exper. Neurol., **9**: 18–28, 1950.
17. Folch-Pi, J. Discussion of partial antigens. Symposium on Experimental Allergic Encephalomyelitis. National Institutes of Health, Bethesda, Md., October, 1957.
18. Freund, J. The effect of paraffin oil and mycobacteria on antibody formation and sensitization; review. Am. J. Clin. Path., **21**: 645–656, 1951.
19. Greenfield, J. G. A form of progressive cerebral sclerosis in infants associated with primary degeneration of the interfascicular glia. Proc. Roy. Soc. Med., **26**: 690–697, 1933.
20. Hallervorden, J. Die Histopathologie der multiplen Sklerose bei Menschen und Tieren. Proc. First Internat. Cong. Neuropath., Rome, **1**: 81, 1952.
21. Hyllestedt, K. Retrobulbar neuritis and disseminated sclerosis. Ugesk. laegr., **112**: 853–865, 1950. (Quoted in Ref. No. 30)
22. Jervis, G. A., Ferraro, A., Kopeloff, L. and Kopeloff, N. Neuropathologic changes associated with experimental cerebral anaphylaxis in the monkey. Arch. Neurol. & Psychiat., **45**: 733–751, 1941.
23. Kabat, E. Wolf, A. and Bezer, A. E. The rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injections of heterologous and homologous brain tissue with adjuvants. J. Exper. Med., **85**: 117–130, 1947.
24. Kies, M. W., Alvord, E. C., Jr. and Roboz, E. Communication at the Third International Congress of Neuropathology. Brussels, Belgium, July, 1957.
25. Koprowski, H., Jervis, G. A., James, T. R., Burkhart, R. I. and Popensick, J. C. A study of canine encephalitis. Am. J. Hyg., **51**: 63–75, 1950.
26. Lander, H. A case of acute hemorrhagic leucoencephalitis (Hurst) complicating varicella. J. Path. & Bact., **70**: 157–165, 1955.
27. Lumsden, C. E. Chapter on pathology. In McAlpine, D., Compston, N. D. and Lumsden, C. E. *Multiple Sclerosis*. Williams & Wilkins, Baltimore, 1955.
28. McAlpine, D. Acute disseminated encephalomyelitis; Its sequelae and relationship to disseminated sclerosis. Lancet, **1**: 846–852, 1931.
29. McAlpine, D. The problem of disseminated sclerosis. Brain, **69**: 233–250, 1946.
30. McAlpine, D., Compston, N. D. and Lumsden, C. E. *Multiple Sclerosis*. Williams & Wilkins, Baltimore, 1955.
31. Macchi, G. Sulla localizzazione perivenose e sulle modalita di accrescimento e diffusione delle lesioni demielinizzanti nella sclerosi a placche. Riv. Pat. Nerv. **75**: 627–662, 1954.
32. Margulis, M. S., Solviev, V. D. and Shubladze, A. K. Etiology and pathogenesis of acute sporadic disseminated encephalomyelitis and multiple sclerosis. J. Neurol. Neurosurg. & Psychiat., **9**: 63–74, 1946.
33. Miller, H. G. and Evans, M. J. Prognosis in acute disseminated encephalomyelitis, with note on neuromyelitis optica. Quart. J. Med., **22**: 347–379, 1952.
34. Morgan, I. M. Allergic encephalomyelitis in monkeys in response to injection of normal monkey tissue. J. Exper. Med., **85**: 131–140, 1947.
35. Müller, R. Studies on disseminated sclerosis. Acta med. scandinav. **133**: (supp. 222) 1–214, 1949.
36. Paterson, P. Y. Presentation at the Symposium on Experimental Allergic Encephalomyelitis. National Institutes of Health, Bethesda, Maryland, October, 1957.
37. Pette, H. Ueber die Pathogenese der multiplen Sklerose. Deutsche Ztschr. f. Nervenh., **105**: 76–132, 1928.
38. Rivers, T. M. and Schwentker, F. F. Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys. J. Exper. Med., **61**: 689–702, 1935.
39. Sabin, A. Discussion at American Association for Neuropathologists, Annual Meeting. Atlantic City, June, 1958.
40. Schaltenbrand, G. *Die Multiple Sklerose des Menschen*. G. Thieme Verlag, Leipzig, 1943.
41. Scherer, J. H. and Collet. Contribution à la neuropathologie du chien. J. belge neurol. et de psychiat., **39**: 132, 1939.
42. Steiner, G. Demonstration von Spirochäten in menschlichen Gehirn bei multipler Sklerose.

Deutsche Ztschr. f. Nervenh., **107**: 112–123, 1928.

43. Störtebecker, T. P. Common infections in disseminated sclerosis and other diseases of the nervous system. Acta med. scandinav., **140**: 41–51, 1951.
44. Stout, R. E. and Karnosh, L. J. Acute disseminated encephalomyelitis. J. A. M. A., **101**: 667–672, 1933.
45. Thygessen, P. Prognosis ved sclerosis disseminata. Nord. med., **35**: 1779–1788, 1947. (Quoted in Ref. No. 30)
46. Thygessen, P. Prognosis in initial stage of disseminated primary demyelinating diseases of the central nervous tissue. Arch. Neurol. & Psychiat., **61**: 339–351, 1949.
47. Trevan, D. J. Discussion of the topic "Demyelinating disease". In Proc. First Internat. Cong. Neuropath., Rome, 1952.
48. Uchimura, L. and Skiraki, H. A contribution to the classification and the pathogenesis of demyelinating encephalomyelitis. J. Neuropath. & Exper. Neurol., **16**: 139–203, 1957.
49. Waksman, B. H. Paper on prevention of experimental allergic encephalomyelitis. To be published in J. Neuropath. & Exper. Neurol., July, 1959.
50. Zimmerman, H. M. Discussion at the Symposium on Experimental Allergic Encephalomyelitis. National Institutes of Health, Bethesda, Maryland, October, 1957.
51. Zimmerman, H. M. and Netsky, M. Pathology of multiple sclerosis and the demyelinating diseases. A. Res. Nerv. & Ment. Dis., Proc., **28**: 271–312, 1950.

ON SUBLIMINAL ACTIVATION

GEORGE S. KLEIN, PH.D.[1]

I am sure that the flood of claims and counterclaims regarding the alleged power of the subliminal must have stirred in you as it did in me mixed feelings of amusement, bemusement and irritation. Anxieties have been fanned, and the public clamor for shelters against the subliminal bombs is beginning to exceed pleas for protection against the far more tangible, real thing. Madison Avenue, flushed with its successes in Washington, squints with alternate trepidation and barely concealed fascination at this possibly new frontier. The Brave New World seems at hand, with Aldous Huxley as our prophet. Artful journalists, pressured to produce one benzedrine effect upon another in their blasé readers, have swelled the tide to a point where in this International Geophysical Year fantasies about *inner* space threaten to carry the day.

Reactions to the claims have appealed more to morality than to fact and theory. In this respect, something of a decisive tour de force was achieved in a shrewdly funny fantasy by a writer for *Punch*. He envisioned the typical movie program of the future—at a drive-in, no doubt—where the main attraction is an hour and a half long feature film consisting of a string of luridly colored advertisements for fancy-finned automobiles, soap, cigarettes, and other bonbons for which advertisers tell us life is worth living. Out front, the audience, clapping for joy at their first views of the chrome-plated monsters, happily settle back in their seats, rhythmically chomping away at a limitless supply of popcorn, and swilling pop (vended automatically, of course, at each car seat). But lo! Far back in the isolated projection room, tense with fear and working a second projector smuggled in from Big Brother's pervasive eye, the lone idealist does his dirty work: between the frames, at exposures of a thousandth of a second, flash by flash, he unfolds—Shakespeare's Othello! The fantasy brings us full circle to that most banal of truths from which moral controversy about science usually begins and where it inevitably ends: that the uses of science's products only reflect, they do not determine, the love or the hate in man's heart.

I find this thought neither interesting nor even elevating by now. For psychologists, the issues concerned in so-called subliminal, or as I prefer to call it, incidental stimulation, are far more fascinating and contain a far greater potential of fresh discovery if we stay within the confines of theory (scientific, not moral), of fact, and of deductions from theory and fact. That is where I propose to stay.

It would be nice to be able to say that the claims for the hidden stimulus have already been lifted out of the murky fog of moral argument and assessed against authoritative reflections on appropriate theory and facts. But the professional discussions I have read on the matter have not been very helpful. Most of the comments have fired justified blasts at the obvious holes in research design—the perhaps fantasied research designs—in which the get-rich-quick entrepreneurs of the subliminal have couched their claims. Insofar as the experts have ventured into theory and previous research, they have leaned heavily upon studies of discrimination without awareness and of so-called perceptual defense. These studies are,

[1] Research Center for Mental Health, New York University, Washington Square, New York. This paper was originally presented at a symposium on The Social Scientist and Subliminal Stimulation, at the Annual Meeting of the American Psychological Association, Washington, D.C., September, 1958. It is based upon experiments supported by grants from the National Institutes of Health and the Ford Foundation.

to be sure, among the more fashionable preoccupations of psychologists these days, but unfortunately they miss the main issues. For whatever the commercial validity of the recent claims—and I predict flatly it will be proved to be nil—the issues raised by them are genuinely novel and important. And these issues, far from being illuminated by the hundreds of studies of discrimination without awareness and perceptual defense, have actually been obscured by them.

The basic issues lurking in the background of all the recent claims are:

a) that an incidental stimulus may activate meanings (or trace systems or schema) quite *independently* of those which are pertinent to the main directions of a person's thought at the moment;

b) that such incidentally or even subliminally activated meanings will affect *different* levels of behavior and *different* modes of experience than the ones to which conscious selective effort is directed;

c) that the incidentally or subliminally activated meanings may have *delayed* effects; they may persist and affect behavior in situations and in states of consciousness quite removed from those in which the excitations originally occurred;

d) that such incidental stimuli may acquire special properties by the very fact of their peripheral status in the field of stimulation, making it possible for such subliminal activations to have *distinctive* effects on thought as compared to stimuli which claim full attention.

Now, there *is* a pertinent literature and there *are* current studies, and there *are* leads provided by theory which do bear directly on these issues. But in the two most recently published reviews (1, 16), one of them directly stimulated by the commercially provoked hubbub, I have looked in vain for any sign of recognition of this literature. I am referring to a line of empirical and theoretical development having shadowy origins in early work by Binet (4), Urbantschitsch (24) and others, which was brought to a focus in Freud's discovery of the day-residue in dreams, and given renewed experimental life by Otto Poetzl's pioneer experiments in 1917 (18), later by Allers and Teler (2), and recently by Fisher (9, 10), Shevrin and Luborsky (22), and by my colleagues at the Research Center for Mental Health (8, 15, 17, 23). And for theory there are available to us the general propositions of psychoanalytic behavior theory, capsuled in Freud's Chapter VII of the *Interpretation of Dreams*, modified, extended, and amplified in many directions pertinent to the main issues by Hartmann (13), Rapaport (19, 20, 21), and others.

I have said that perspective has been wizened and important phenomena obscured by restricting questions about subliminal stimulation to the issue of whether or not discrimination is possible without awareness—a favorite query of the last few years. The questions in such studies usually involve two considerations: the degree to which an experience—a discrimination, a recognition, a conditioned response, a choice—is swayed by contiguous stimuli presented at levels where no verbal recognition is possible; secondly, the extent of S's unawareness of the allegedly subliminal stimulus. Study after study has hovered over this second point: to what extent was S actually aware of at least *some* feature of the stimulus.

So far as an *experience of discrimination* is concerned, where a subject actively engages in an attempt to identify accurately a portion of a stimulus field, the evidence seems indeed to weigh heavily *against* the discriminability of a stimulus when no part of it is conscious. Discrimination distinctly improves as intensity of a stimulus increases, *i.e.*, as S has more consciously available pegs on which to anchor hypotheses as to what is "out there." It seems clear from the convincing studies by Bricker and Chapanis (6), Voor (25), and Boardman (5) and others that it is impossible to discriminate—in this sense of an *intention to identify*—a part of the field without having

some partial conscious information from the stimulus to go by. These studies tell us that previous claims for discrimination without awareness may have been based upon an artifact, an insufficient sampling of the *partial* information that subjects were aware of on the basis of which they made better-than-chance discriminations of stimuli.

These critics have done us a valuable service in showing that we need not assume two kinds of discrimination, but only one. However, their conclusions in this respect teeter on the edge of over-generalization because of an argument which runs something like this: Only a discriminated stimulus can affect thought, and discrimination always depends upon at least some information being within the subject's conscious grasp. Without some positive awareness of a stimulus, there is no effect.

This argument suffers from a chronic ailment of many psychological explanations: it overlooks the subject's intentions. How much a person must *consciously* apprehend of the many stimulus excitations which enmesh themselves in his behavior is a relative matter, depending very much on what he is trying to do and what the situation requires of him. Different requirements are set in this respect when a person is actively *trying* to penetrate a field of stimulation—when his *aim* is discrimination—than when he is, say, conjuring a daydream to escape the dreariness of a lecture on subliminal stimulation. Awareness is most of the time foreshortened, and it had better well be. That socks, shoes, and trousers get put on in the morning, that these acts be *performed*, is the main thing, and not that we be *aware* of the movements or of the order of movements involved. A discrimination *task* in the laboratory lays down a *special* requirement: that S report effectively and accurately on what is "out there." Sometimes this requirement is explicit in instructions; almost invariably S himself assumes it as soon as he is asked to tell what something *is*. Such an intention to discriminate is not a simple matter involving perception alone. It is a complex orientation in which attention is finely tuned to the promptings of expectations and sets, aided and abetted by postural and muscular adjustments—all mobilized to the aimed-for effectiveness and accuracy. Communicated response is governed by standards of adequacy (and these standards need not be conscious). In this type of context it is easy to understand the importance of a *perceivable* cue or signal; molding a *reliable* hypothesis and meeting subjective standards of adequate response would require it to a certain minimal degree, a minimum which probably varies among people and with different "cognitive styles." It reduces the range of the improbable; it helps establish a hierarchy within the range of the possible.

The only point proved, then, by the critics is that an *intention to discriminate*, in Brentano's sense of a particular kind of orientation to a stimulus, cannot be successfully implemented until some critical, minimal segment of the field is consciously apprehensible. But we must be careful where we carry this conclusion. From the fact that an incidental or subliminal stimulus is inadequate for discrimination, we cannot conclude that it has provoked *no* activating effects at all, effects not reflected in the discrimination responses, and that it was effaced as quickly as it was written, if it was written at all. Nor can we infer from the demands of discrimination that *all* behavior contexts and confrontations with stimuli will make similar claims for consciously accessible information.

Does the fact that *identifying* a stimulus requires at least some partial conscious information rule out the possibility that *some* information has been transmitted or, in fashionable terminology, encoded and ordered into schemata without awareness of it? Such a conclusion would be patently absurd. It requires no experimental demonstration to say confidently that we are not aware of all the stimuli which we use in be-

havior. This sort of thing happens constantly in perception. We recognize a face without noting the specific features; we throw and catch balls when their trajectories are far too complex for a physicist to predict. People usually know nothing of such cues as binaural time differences, yet they use them constantly and with excellent effect in perceiving the locus of sounds. Constancy phenomena testify to the same thing. The issue, in short, is not whether the subliminal can affect behavior, but 1) whether or not the subliminal impact is observable in some variation of conscious experience which need not necessarily be an act of discrimination; 2) whether or not it has an *independent* status in the sense that its cognitive effects run parallel to, without intruding upon, a *concurrent* act of discrimination; 3) whether or not its effects are discernible in some other situations or behavior; and 4) whether or not it is itself recoverable to consciousness under conditions where the usual premises of reality testing are in abeyance. It would help, therefore, if we were careful in separating the fact of *activation* from the *varieties of experience* in which the effects of activation are embedded.

This point is made in recent experiments carried out by Franklin Goldberg and Harry Fiss, and by Benjamin Lapkin and Paul Lippmann, at the Research Center for Mental Health in New York. The Goldberg and Fiss experiment is particularly apropos because it grew out of an effort to test for discrimination without awareness. Their study shows that even though a discrimination of a stimulus is not possible, the stimulus may still have an activating effect and may influence the course of another kind of experience, for instance, *imagery*. They tested the Bricker and Chapanis hypothesis directly under conditions where a person knew clearly that his task was to discriminate and what the figures were that he was to try to tell apart. In the first part of the experiment, either a triangle, a circle, or a square was briefly exposed in a fixed random order; the exposures were gradually lengthened until parts of the figures were clearly discernible. Each time a figure was flashed, the subject was required to say *what* he saw —any small part, a blur, or a mere flicker. In addition, he had to *guess* which figure had been shown (knowing it had to be one of the three). This guess the subject made on every trial, even if all he could actually report seeing was the merest flicker or shadow. It was found that at those levels of exposure where only a flicker or an unformed blur was reportable, guesses (discriminations) were no better than chance. When exposures reached levels where some *partial* recognition of a figure was possible at least part of the time, success in identifying the whole figure increased, but reached only marginal levels of significance. Only when stimulus exposures were long enough to make some part of the figure clearly perceptible were the subjects' guesses about the identity of the whole figure clearly better than chance.

We have here further substantiation of Bricker and Chapanis' main point, that a successful discrimination experience is not possible unless the subject has some conscious grasp of a portion of the stimulus he is trying to discriminate. This should not be surprising. Discrimination under laboratory conditions is guided by an attitude which we know as "reality testing." The subject prefers to work with information that can be consciously assessed and incorporated into a reasonable projection of the actual structure of objects and events. An effort to discriminate becomes a disciplined encounter with a field of stimulation for which *perceived* data have preeminent status. Its outcome is a distinct kind of discrimination *experience* with laws of its own.

But the experimenters carried the matter further. May not these low level stimuli, they asked, exert an influence upon some form of experience other than discrimination? The fact that the stimuli are wanting

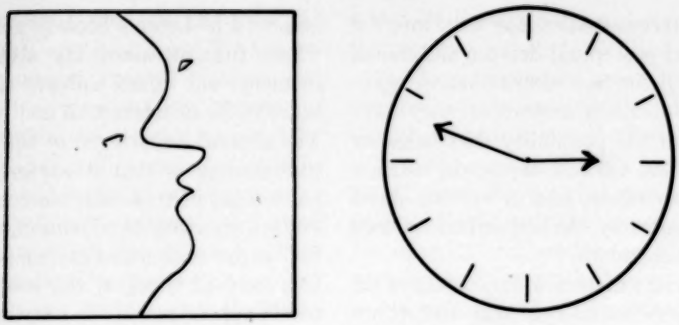

FIG. 1. Double profile and clock stimuli described in text.

for the requirement of effective discrimination experience does not touch the issue of whether or not they may register anyway and have a modifying effect on behavior and other types of experience. They tested this possibility. Taking the square, they contoured its interior to form a double profile; within the circle they drew a clock (Figure 1). They then exposed each of these figures to the same subjects at an exposure time well below the level which in the discrimination experiment had provoked at most only reports of flicker in response to the square and circle. They exposed the clock figure twice at this brief exposure. Immediately after, they asked the subjects to report any spontaneously occurring *images* and to draw them as best they could, following a procedure recently employed by Fisher and Paul (10) and used earlier by Allers and Teler (2). Then, the double profile picture was exposed at the same exposure level, again with a request for images and drawings. It now remained to see whether there was a significant intrusion of the double profile picture in the one set of images and of the clock in the other. Of course, the subjects didn't know that their images were to be studied in this fashion. They believed they were engaged in a different experiment—one on imagery—having nothing to do with the earlier discrimination task.

The effects were assessed in two ways, first, by having judges evaluate the drawn images against the characteristics of the stimuli, and then to pair each drawing to its probable stimulus; and second, by assessing this similarity quantitatively according to a checklist of double profile and clock properties developed in the prior independent study by Fisher and Paul. The results were decisive. Five of the six judges showed a preponderance of correct placements of the images for the stimuli. On the checklist, images produced after the double-profile exposure showed a significant preponderance of double-profile elements compared to images elicited by the clock stimulus. Incidentally, a subsequent check of the *discriminability* of the two stimuli—that is, when Ss were asked to guess, after a given exposure at the same exposure time of the original experiment, whether the clock or the double-profile had been shown—produced no significantly successful discrimination responses.

The experiment indicates that a direct effort to discriminate a sector of a stimulus is indeed not possible unless some level of information is consciously accessible. It is equally decisive in showing that low level stimuli may nevertheless register; that they contribute to the organization of a sequence of thought (in "schemata" or "trace systems"), and that this activity is discernible when we look for it *not* in an actual discrimination task but in some other variety of experience—an act of imagery relatively free from the vigilant eye of "reality testing."

In short, recent studies may have interred the corpse of perceptual defense and muted claims for distinctive discriminative agencies in an outside of awareness; they have not ruled out the possibility that behavior is affected on various levels, in various modes of experience, and in various states of consciousness by the activations induced by subliminal stimuli.

To appreciate these new dimensions of the problem of subliminal and incidental stimulation, it is helpful to take a closer look at the older, neglected studies. On the whole they provide more telling examples of subliminally induced cognitive activity than do most of the hundreds of recent studies which carry the additional burden of a tortuously unwieldy and theoretically shabby concept of perceptual defense. The Goldberg and Fiss study just cited is only one of a line taking its cues from Binet, Urbantschitsch and Freud. These earlier studies are important because they directly concern the issue of the delayed impact of incidental registration, and because they raise the possibility that incidental stimuli acquire unique properties and affect thought in distinctive ways by virtue of the fact that they *are* incidental, that they *are* in the background of the stimulus field, that they do *not* command attention, and that they by-pass the critical assessments made possible by consciousness.

I should like briefly to draw attention to Freud's observations on the day-residue in dreams, the significance of which has not been fully appreciated in contemporary experimental psychology. The phenomenon of the day-residue involves the carryover into dreams of incidental registrations of recent events. Freud gives many examples of fleeting daytime experiences that had captured hardly any notice at all, yet became prominent carriers of a dream's action that night. He remarks about his dream of a botanical monograph: "The first of these two impressions with which the dream was connected was an indifferent one, a subsidiary circumstance: I had seen a book in a shop window whose title attracted my attention for a moment, but whose subject matter could scarcely be of interest to me" (11, p. 174). The general importance of the day-residue phenomenon is that it concerns the effect on thought of transient, momentarily unessential, even unnoticed stimuli, which nevertheless are drawn into an independently active field of thought, the consequences of which appear not in the occasion where the activation took place but only later in a dream. Freud made much of this remarkable fact that dream content draws upon the trivial impression or passing glimpse. He suggested further that such "indifferent" perceptions, as he called them, have a distinctive role in the workings of the dream, perhaps significantly different from those of focal impressions and perceptions, that is, registrations that we *are* aware of and to which we directly respond in the ordinary course of the waking day. "Dreams," he said, "have a preference for taking up unimportant details of waking life" (11).

Otto Poetzl's experiments in 1917 (18) were the first attempt to deal experimentally with the day-residue phenomenon. It is interesting to note, in view of the well known contempt in which Freud held early experimental psychology, that these experiments were among the few that Freud was genuinely attracted to and that he expressed enthusiasm for the method used. Using a tachistoscopic technique, Poetzl demonstrated that the manifest content of dreams incorporated elements of the briefly exposed stimuli of which a person had never been conscious. After showing his subjects landscapes very briefly for about a hundredth of a second he had them describe and draw what they had seen. To an extraordinary degree, what was not reported by him showed up in the subject's account and drawings of dreams he had the night following the tachistoscopic exposure.

I cannot here go into the more recent, better controlled, more carefully detailed stud-

ies by Fisher and Paul (10), Shevrin and Luborsky (22), and others which have refined and extended Poetzl's method, and which have developed striking support for his main conclusions. Recent studies have been broadened to include different possible loci of effects and modes of experience other than perceptual, *e.g.*, imagery, and other states of consciousness besides dreams. They have also expanded to include an interest in *transient stimuli* of all kinds so that there is now a tendency to regard the so-called subliminal stimulus as but a special, perhaps extreme case, of incidental stimulation. (17). All these studies also involve distinct advances in method over the well known "recognition threshold" technique which has figured so prominently in studies of discrimination without awareness and of perceptual defense. Perhaps the most important feature of these studies is that they are framing questions about incidental stimuli from vantage points provided by the general psychoanalytic theory of behavior. Not from a concept here or a concept there culled in isolated fashion from the theory, the rest banked off by heavy coatings of vitriol, but with attention to implications of links among concepts within the theory. How the logic of inquiry is conditioned and enriched by this commitment is too long a story to recount in this paper. Let me simply remark that the problem of incidental stimuli is illuminated in fresh and productive ways by such interlocking considerations from psychoanalytic theory as its propositions concerning attention-cathexis, the relative participation in thought of controls, defenses, and drive; regression; activity and passivity; reality testing, and varieties of conscious experience.

The recent studies have centered upon the following questions:

1) How and in what different ways do incidental stimuli affect conscious experience and other behavior, and within what limits?

2) What are the circumstances—the structural conditions of consciousness—in which such activations of meaning emerge into conscious thought and behavior?

3) Do the incidental activations have distinctive effects on thought compared to stimuli which claim full attention?

It is of course impossible for me to dwell at all upon the detailed findings that are now available on these issues. The results are complex and subtle; the effects depend upon a great many variables such as associative connotations of the stimuli, the conscious intentions, state of consciousness and passivity of the subject. I can only draw attention to certain main points of convergence in the findings. 1) It is now quite clear that an incidental stimulus may be enlisted in a train of thought quite independent of the task at hand, and its effects may or may not be immediately observable in the task a person is engaged in, but may be *delayed*, and show themselves on levels of behavior and in states of consciousness bearing little similarity to the original context of stimulation and report. For those who like to be reassured about the condition of their psychological pie by checking it against the standards of neurological chefs may I point out in passing that recent discoveries regarding reticular structures lend encouragement to the conclusion that activations may occur independently of concurrent perceptual experience. 2) The findings emphasize the importance of separating the *activating* effects of a stimulus from the modes of *experience* in which the stimulus may come to awareness. Perception is only one of various possible modalities of experience, and it is only one of several ways in which we may become aware of a subliminally activated meaning.

Another implication emerges from results of recent studies. It seems to me more valuable to refer to the generic event in all these studies as *incidental* stimuli rather than as subliminal stimuli. The latter term would better refer to certain operational means of rendering stimuli incidental in various contexts. The importance of a stim-

ulus is not so much its subliminal status as the meanings and properties it acquires when circumstances relegate it to the periphery of conscious thought and attention. Awareness of a stimulus increases the possibility of its being subjected to the disciplined categorizing and assessment which are characteristic of adaptive thinking. It is for this reason that it has seemed to me less important to ask: How far below awareness can stimulation occur and still produce an effect upon behavior, as to ask: In what ways and for what reasons does *increased awareness* of a stimulus lead to *changes* in thought and behavior?

A critical consideration in assessing the effects of incidental stimuli are the conditions of *control* which characterize any particular state of consciousness. Again here psychoanalytically-derived propositions concerning reality testing and attention, and the balance of drive and control are especially helpful (14, 19). In certain states of consciousness the incidentally activated material may emerge in awareness in the context of images while perceptions will show little evidences of it. Dreams, hypnosis, hypnogogic and mescalin states perhaps enable a relatively undifferentiated slice of incidentally registered experience to be re-experienced with an intensity which in the usual waking state of the laboratory can be accomplished only through passive, eidetic-like imagery. As reality contact and reality requirements are minimized, so the prospects of incidentally registered material emerging to awareness in passive imagery may increase.

In view of these considerations, it should not surprise us that the behavioral effects of subliminal or incidental stimulation are *small*, insofar as these effects have been sought in the behavior of *waking states*, and that such effects can be highlighted only under conditions where critical judgment and reality testing are bypassed. Anyone working on the problem of incidental stimulation would do well to give up any notions that the effects will be huge, clearly explicit on just *any* level of response and in any task. The very forces that render a stimulus incidental to begin with render them also incidental in their effects on behavior, at least under the conditions of reality appraisal and pragmatic considerations which ordinarily characterize waking life. But certain corollary implications are equally important: conditions of induced passivity, reduced reality testing and reduced activity in thought—concepts which to my mind are crucial to a general theory of cognitive behavior—will also enhance the effects of the incidental stimulus on thought and behavior.

A word in conclusion about the so-called practical side of all this research. It is surely cavalier to hope that a subliminal stimulus will preserve in its vicissitudes in peripheral thought the *single* meaning which the advertiser desires it to have, that it will produce a *specific* effect consonant with this particular meaning on the *one* level that the advertiser is likely to be interested in —activity in the region of the pocketbook. There is no reason to expect a single impact on a single level any more than there is reason to expect a this for a *supra*liminal stimulus. A comforting paradox confronts us here: that reality testing which so constricts awareness in the sense that it elides from our attention a great number of object properties having no bearing on the pragmatics of everyday life, has also a protective outcome. This same reality sense and reality testing prevent just any stimulus from exerting an uncheckable influence on behavior. Enslaved we always are, by ideas, by what people do to and for us, by the activations—supraliminal and subliminal—which these provoke. But a curiously indomitable element of critical choice and delay intervenes in the selection of our masters, setting the terms of our enslavement by them on various levels of behavior and in different occasions of behaving. It is an

element which is muted only by extreme changes an our reality sensibility.

REFERENCES

1. Adams, J. K. Laboratory studies of behavior without awareness. Psychol. Bull., **54:** 383–405, 1957.
2. Allers, R. and Teler, I. Ueber die Verwertung umbemerkter Eindruecke bei Associatonen. (Trans. made available by courtesy of Mrs. Ruth Ohlin.) Ztschr. f. Neurol. und Psychiat., **89:** 492–513, 1924.
3. Bach, S. and Klein, G. S. Conscious effects of prolonged subliminal exposures of words. Amer. Psychologist, **12:** 397, 1957.
4. Binet, A. *Alterations of personality.* (Transl. by Helen G. Baldwin.) Appleton & Co., New York, 1896.
5. Boardman, W. K. Utilization of word structure in prerecognition responses. J. Pers., **25:** 672–685, 1957.
6. Bricker, P. D. and Chapanis, A. Do incorrectly perceived tachistoscopic stimuli convey some information? Psychol. Rev., **60:** 181–188, 1953.
7. Dixon, N. F. The effect of subliminal stimulation upon autonomic and verbal behavior. J. abnorm. soc. Psychol., **57:** 29–36, 1958.
8. Eagle. M. The effects of subliminal stimuli of aggressive content upon conscious cognition. Ph.D. dissertation, on file New York Univer. Library, 1958.
9. Fisher, C. Dreams and perception. J. Amer. Psychoanalytic Ass., **3:** 389–445, 1954.
10. Fisher, C. and Paul, I. H. The effect of subliminal visual stimulation on imagery and dreams: A validation study. J. Amer. Psychoanalytic Ass., **7:** 35–83, 1959.
11. Freud, S. *The Interpretation of Dreams.* Vol. V, Chap. 7. The standard edition of the complete psychological works of Sigmund Freud. (Transl. by J. Strachey.) Hogarth Press, London, 1953. (Originally published in 1900.)
12. Goldberg, F., Fiss, H., and Klein, G. S. Effects of undiscriminated stimuli upon imagery. (Submitted for publication to J. abnorm. soc. Psychol.)
13. Hartmann, H. Ich-Psychologie und Anpassungsproblem. Int. Z. Psychonal., **24:** 62–135, 1939. (Translation, Ego psychology and the problems of adaptation [abridged]. In D. Rapaport [ed.], *Organization and Pathology of Thought.* Columbia Univer. Press, New York, 1951. Pp. 362–396.)
14. Klein, G. S. Consciousness in psychoanalytic theory: Some implications for current research in perception. J. Amer. Psychoanalytic Ass., **7:** 5–34, 1959.
15. Klein, G. S., Spence, D. P., Holt, R. R. and Gourevitch, Susannah. Cognition without awareness: Subliminal influences upon conscious thought. J. abnorm. soc. Psychol., **57:** 255–266, 1958.
16. McConnell, J. V., Cutler, R. L. and McNeil, E. B. Subliminal stimulation: An overview. Amer. Psychologist, **13:** 229–242, 1958.
17. Pine, F. Incidental stimulation: A study of preconscious transformations. J. abnorm. soc. Psychol. In press.
18. Poetzl, O. Experimentally provoked dream visions in their relations to indirect vision. ("Experimentell erregte Traumbilder in ihren Reziehungen zum indirekten Sehen.") Z. Neurol. Psychiatr., **37:** 278–349, 1917.
19. Rapaport, D. Cognitive structures. In J. S. Bruner, *et al. Contemporary Approaches to Cognition,* pp. 157–200. Harvard Univer. Press, Cambridge, 1957.
20. Rapaport, D. The theory of ego autonomy; A generalization. Bull. Menninger Clin., **22:** 13–35, 1958.
21. Rapaport, D. Structure of psychoanalytic theory: A systematizing attempt. To be published; Amer. Psychol. Ass. Project A. McGraw-Hill, New York, 1959.
22. Shevrin, H. and Luborsky, L. The measurement of preconscious perception in dreams and images: An investigation of the Poetzl phenomenon. J. abnorm. soc. Psychol., **56:** 285–294, 1958.
23. Smith, G. J. W., Spence, D. P., and Klein, G. S. Subliminal effects of verbal stimuli. Amer. Psychologist, **12:** 394, 1957. (J. abnorm. soc. Psychol., in press.)
24. Urbantschitsch, V. *Uber subjective Optische Anschauungsbilber. (Subjective optical imagery.* Transl. by S. Bach.) Vienna, 1907.
25. Voor, J. H. Subliminal perception and subception. J. Psychol., **41:** 437–458, 1956.

SEMANTIC APHASIA: II

WALTHER RIESE, M.D.[1]

INTRODUCTION

Of the four varieties of aphasia distinguished by Head (5), semantic aphasia has proved to be the least known and the least popular. In fact, semantic aphasia is rarely mentioned in textbooks, monographs or papers dealing with speech defects resulting from brain lesions. One reason for the surprising lack of observational data may be found in the fact that semantic aphasia is the only one of the four varieties distinguished by Head which cannot be projected on the existing varieties and traditional terms. Moreover, as stated by this writer in his first investigation of the subject (6), a number of still unsettled problems of great scope is implied in semantic aphasia, above all that of the interrelation of language and thought and the correlation of language disorders with brain lesions, their sites and types.[2]

THE TYPE OF THE DISORDER AND THE SITE OF THE LESION

In Head's own terms, semantic aphasia leaves unaffected the crude acts of speaking, reading and writing. Patients suffer from no difficulty in pronunciation; syntax and intonation remain undisturbed, they are able to repeat, and as a rule, to name and indicate common objects. It is the *comprehension of the significance of words and phrases as a whole which is primarily disturbed.* The fault is essentially *a want of recognition of relative significance and intention.* Everything tends to be appreciated in detail, but the general significance is lacking. These patients become confused over the general principles underlying some act or idea. Moreover, *orientation* is more or less gravely affected, patients being completely unable to find their way alone, unless they pass automatically from place to place.

Head's *localization* of the lesions was not based on post-mortem examinations, but on an ingenious reconstruction on the cadaver. Brain injuries in Head's cases of semantic aphasia were diffuse, but the main lesion was found behind the post-central fissure, in the neighborhood of the *supramarginal gyrus* and the superior parietal lobule.

The reader familiar with Goldstein's writings will have little doubt that the basic disturbance revealed by individuals suffering from semantic aphasia, is that of an "impairment of abstract attitude"; significant, it is true, of brain damage at large, whether frontal, parietal, insular or even diffuse. Goldstein has shown this on many occasions. It would be impossible, were it only for reasons of space, to list all publications in which Goldstein described the differences between abstract and concrete attitude and its bearing on the interpretation of behavioral disturbances resulting from brain lesions. The reader is referred to one of Goldstein's most comprehensive and didactic though less known presentations, "The effect of brain damage on the per-

[1] The Medical College of Virginia and the Eastern State Hospital, Williamsburg, Virginia. This paper is written as a tribute to Kurt Goldstein on the occasion of his eightieth birthday (November 6, 1958). The author is happy to acknowledge his debt to a great teacher and friend.

[2] As with so many aphasics, the patient whose history and brain lesions are here reported and analyzed, was supposed to be demented and for this reason committed to a mental hospital. Under the circumstances his aphasia could not be tested according to rules. Not until this writer was shown the brain was the diagnosis of semantic aphasia reached, *i.e.* post mortem, after inspection of the brain and the site of the lesion found. The writer then reconstructed the still somewhat fragmentary history of aphasia out of clinical notes and the result of a comprehensive interview to which he submitted the surviving wife of the patient. Experienced consultants not infrequently face such situations; they may then either forego the analysis of at times very precious cases or follow the procedure adopted and outlined by the writer.

sonality" (4). It is for similar reasons that this writer raised the question whether the variety of aphasia here considered can still be classified with speech defects. But since the interrelation of speech and thought is particularly conspicuous in the variety under discussion—patients failing in all tests implying inner verbalization—this group may still be considered as a variety of aphasia.

In the first case of semantic aphasia in which a complete examination of the brain was made (6), lesions were vascular, diffuse, and multiple, the left hemisphere nevertheless being the site of a large destroying focus of encephalomalacia, involving the left inferior parietal lobe, and in particular the major part of the left gyrus supramarginalis. Excluding, though somewhat reluctantly, the multiple and mostly minute lesions found in both hemispheres from the attempt to correlate the semantic disorder with a well-defined brain lesion, the destroying lesion of the inferior parietal lobe still emerged from the study of my first case as the major structural condition of semantic aphasia.

REPORT OF THE SECOND KNOWN CASE OF SEMANTIC APHASIA WITH COMPLETE EXAMINATION OF THE BRAIN

This patient was believed to have suffered a number of minor strokes, the first at the age of 65. All these strokes were described as similar to each other, all of them affecting his speech and motor power. Attacks lasted, as a rule, about five to ten minutes. Between these attacks, he seemed to have been totally disoriented as to time, place and his own person; unable to remember his name, address and unable to find his way home. Very often he wandered off, and was found and brought home by others. More than once he came home with his underclothes missing and was unable to account for this loss. *He did not always understand when spoken to*, but sometimes could follow simple conversation. He had never been able to read; his wife was not too sure that he had ever been able to write. He was right-handed. He *lost understanding for the meaning of almost everything*,[3] even the meaning of the tree and gifts at Christmas. In the beginning of his illness he could understand jokes which, however, dated back to his early days. Sometimes he would not dress properly, reversing his underwear and putting his shoes on the wrong feet. He had to be bathed and dressed and his plate was served for him; otherwise, he would eat any food, even things that he didn't like;[4] but he never put other objects to his mouth. Finally, his behavior became very childlike. Towards the end, he spoke only when some one addressed him. His memory failed increasingly. Most of the time he was restless, walking and wandering. Sometimes he had bowel movements in his clothes. In the beginning of the illness he was still able to go on errands, but always with a written list unless it was just one item. Money was given to him and he brought home change. He never lost orientation in his own home.[5] At times he went into other homes, without doing anything, apparently under the impression that he was in his own home. He became increasingly helpless and, when taken out of the hospital for a day, did not talk at all, nor did he express any desire or interest. During his stay at Eastern State Hospital, it was repeatedly noticed that he

[3] *i.e.*, everything that implied recognition of the ultimate significance and intention of words and phrases.

[4] In other words, he could carry out a maneuver where each action suggests the next; patients affected by semantic aphasia retain this automatic behavior, but fail if they are compelled to formulate the maneuver by themselves as a whole. It is not "memory" that is affected, but the power to coordinate details into a general formula for internal or external statement.

[5] This statement seems to contradict the previous observation that "between the attacks... he seemed to have been totally disoriented." But it means no more than the fact that semantic aphasia did not reach its most severe form, preventing the patient thus affected from "recognizing landmarks" or from even "appreciating that they are passing over ground that should be familiar" (H. Head).

UNIVERSITY OF MICHIGAN LIBRARIES

was confused and completely disoriented as to time and place. On one occasion, his responses were "very stereotyped," all questions being answered with a single word. Memory was also found to be defective. But confusion and disorientation emerged from the clinical observations as the most significant and lasting disorders. There were bilateral pyramidal signs. The patient died at the age of 69, bronchopneumonia and generalized arteriosclerosis being the major autopsy findings.

GROSS EXAMINATION OF THE BRAIN

The brain weight was found to be 1270 grs. after removal, and 1110 grs. after fixation. The cerebral arteries showed very marked arteriosclerotic changes. A destroying lesion of considerable extent was found in the left hemisphere, involving the posterior part of the first, the second temporal convolutions, and the angular gyrus (Figure 1). The lesion presented itself as a deep groove, the floor of which appeared to be membranous and rich in blood supply. It was found to reach far into the white matter, the wall of the lateral ventricle, however, remaining intact. The calcarine fissure was not involved. A cribiform state was found in the basal ganglia of both hemispheres. No gross lesion could be seen in the brain stem and cerebellum. A minute area of softening was found in the right hemisphere above the anterior commissure and close to the ventricular wall, this area destroying the anterior portion of the pallidum. The pathologic type and multiple occurrence of the major and minor lesions left no doubt as to their vascular nature. Nor was there any doubt that critical areas of speech were involved.

Histological examination revealed the well-known picture of an encephalomalacic cyst at the stage of organization. Numerous granular corpuscles persisted in the wall of the cavity, either in groups or in an isolated

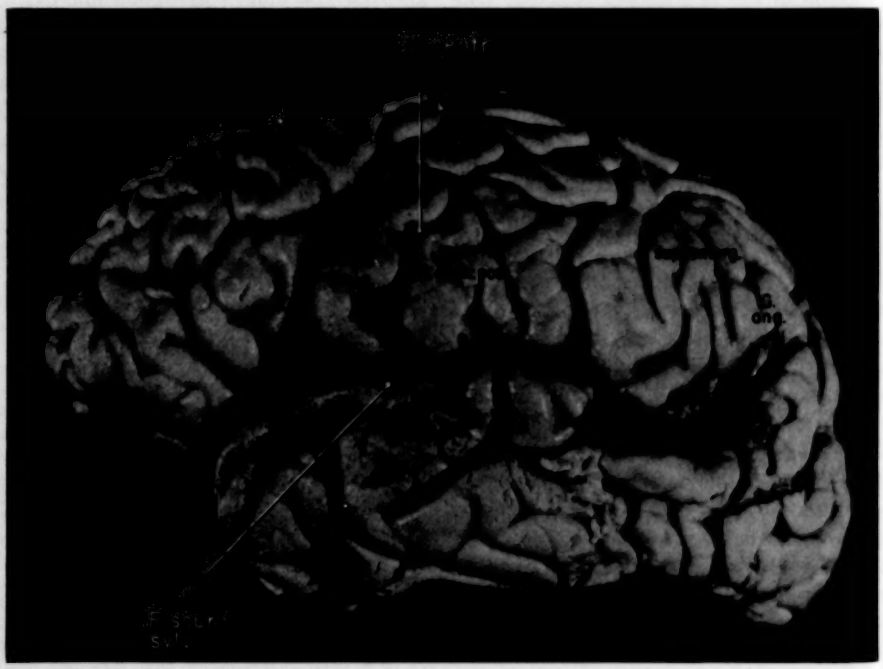

FIG. 1. Lateral view of the left hemisphere.

fashion. The wall of the cyst consisted of a loose connective tissue carrying numerous vessels. Blood pigment within the granular corpuscles was found in a disseminated fashion throughout the softened area and its vicinity, but also in areas far remote from the focus of destruction.

The most remarkable change was a diffuse demyelination extending from the frontal to the occipital areas of the left hemisphere, this demyelination being most marked at the level of the destroying lesion (Figure 2). The right hemisphere also was the site of a diffuse, though less severe demyelination, minute softenings, and a somewhat larger encephalomalacic focus destroying the medial division of the anterior part of the pallidum. The corpus callosum appeared to be reduced in volume; a minute softened area was found in the splenium corporis callosi which also revealed some demyelination.

FIG. 2. Weil stained section at the level of the lesion; note demyelination.

INTERPRETATION

As with the first known case of semantic aphasia in which a complete examination of the brain was possible (6), the lesion proved to be far more extensive than expressed by Head's cautious statement (made on the sole ground of a reconstruction of the site of brain injuries on the cadaver). Insofar as the lesion in our second case involved the inferior parietal lobe of the left hemisphere, it indeed confirmed the tentative localization of Head. Contrary to Head's statement, however, the gyrus supra-marginalis did not emerge as the site of the major lesion which, in our case, was found predominantly to involve the angular gyrus (area 39), posterior temporal areas and adjacent occipital structures (area 19) on the left hemisphere. In addition, wide areas of the left hemisphere were demyelinated. The lesion was a cortical as well as a subcortical one, thus making it difficult, if not impossible, to relate the symbolic disorders observed to a purely cortical site of the lesion. It is this combined appearance of cortical and subcortical lesions, so significant of the majority of destroying and encephalomalacic brain lesions in aged individuals, which provided Head with one of his major arguments against the existence of so-called centers of speech and language, believed by early writers to be confined to the cerebral cortex. According to the same author, the resulting disorder of symbolic thought and expression is more severe, the deeper the lesion extends to the subcortical structures. The pathological, *i.e.* slowly destroying and encephalomalacic nature of the lesion may be said to be responsible for the regional and, above all, the lasting character of the functional defect (7, 8).

Of all cytoarchitectural areas involved in the case here described, area 19, *i.e.* an occipital field, was by far the most severely affected one, large sections of this area being destroyed and undermined by the deep cystlike defect which almost reached the ventricular wall (Figure 3). *The involvement of area 19 appears to mark a new constituent in the structural conditions of semantic aphasia.* It remains true, however,

FIG. 3. Nissl stained section; note large cavity and disrupture of the cortex (area 19).

that none of the cytoarchitectural areas involved was completely destroyed; remnants of areas 39 and 19 could easily be identified. The importance of the amount of tissue destroyed or preserved for the genesis of symptoms was first emphasized, about a century ago, by Flourens. This has been repeatedly stressed by the contemporary experimental neurophysiologist Lashley, and also used by this writer for the interpretation of speech components lost or preserved, in his first case of semantic aphasia. The amount of tissue preserved in our second case evidently was not sufficient to prevent the semantic disorder from coming into being, once a major part of the parieto-temporo-occipital areas was destroyed. Area 40 did not appear to be involved at all, though a small amount of iron brought out in area 40 suggested previous bleedings.

One might still raise the question of the localizing effects of the other lesions found in the case here described. Attention will focus on those disorders of symbolic thought and expression, present in our case, which cannot be considered as reflecting the semantic aspect of language. In fact, the patient finally ceased to talk, thus revealing at the terminal stage "verbal defects" (Head). But none of the lesions discovered in the anterior part of the left hemisphere affected the critical area of speech. Moreover, it seems no longer possible to divide language into several isolated components, each of these components having their individual sites in corresponding cortical areas.

It seems more intelligible to consider language, disturbed or not, as an *integrated* function though analysis and testing admit of different constituents. There is implied in each act of speaking and understanding spoken, written or printed language the whole of an individual's history, past and present, and the whole of his intact or, as in aphasics, remaining power to communicate through symbols, though at different levels, with different means and different success. During his history the individual is likely to use successively *all* cerebral structures for the final building up of his language; this is the meaning of von Monakow's chronogeneous localization. There is also implied in each act of speaking the meaning of the spoken words, this meaning implying the unifying and integrating factor, so obvious in propositional speech. It is this wholeness of symbolic thought and expression which makes intelligible Head's observation that "a severe lesion in appropriate parts of the brain may destroy *all* orderly speech to such an extent that the patient retains the use of a few words only and cannot read or write consecutively . . ." (5, I, p. 220). Above all, Head observed that "time may profoundly change the extent of the loss of function . . . without changing the essential nature of the defects." Head included these statements in the principles one should bear in mind before trying to establish classes of aphasia. Finally, he confessed that each of his own groups "included disorders of wider extent

than those comprised under the name by which it is known" (5, I, p. 219).

These principles do greater justice to man's symbolic thought and expression, to man's wholeness, implied in his communicative power, than the decomposition of language, disturbed or not, into several isolated components, each of them carrying *physiological* names (*e.g.* motor, sensory, visual), each of them thought to be represented separately in well-defined areas of the cortex.

Though it still remains true that speech disturbances resulting from brain lesions may be divided into several groups or varieties,[6] in accordance with the sites of lesions, none of these varieties can properly be described as normal speech minus one (or more) of its components. None of the latter is lost for ever (Jackson remarked that the "speechless man" still has words) and each of them may be recovered according to time and conditions. The flexibility of defects or symptoms, according to time, is reflected by the various stages through which each case of aphasia passes. The flexibility according to conditions or tasks required is embodied in the changing results of the tests to which the aphasic may be submitted in experiment and life. The brain lesion does no more, but also no less than to deprive the injured individual of his faculty to use these various constituents at will and at any chosen moment. Thus is reaffirmed at the highest level of nervous function, the Aristotelian and Galenic idea of the brain as being purely *instrumental* in animal and human life.

The multiplicity of lesions sets limits to our localizing efforts. Of course, nobody would be willing to exclude from these localizing efforts the major lesion, destroying considerable parts of the left parieto-temporo-occipital areas. Nevertheless neither our first nor our second case of semantic aphasia can answer the question as to whether the sole destruction of these areas may result in semantic disorders, since in both cases wide areas of the whole hemisphere were also found to be involved. Moreover, neither the right hemisphere nor the corpus callosum remained unaffected in this second case. The tentative cerebral localization of semantic aphasia reached by Head seemed to favor the left inferior parietal lobe and more particularly, the supramarginal gyrus as the sole site of the lesions. Indeed, in both of our cases this area was included in the destroying though much more extensive lesions. No case of non-traumatic semantic aphasia has as yet come to our knowledge in which complete examination of the brain disclosed but a single lesion limited to the left inferior parietal lobe or even to the sole supramarginal gyrus which Head, deriving his conclusions from the reconstructed site of brain injuries in the living patient, believed to be involved selectively in semantic aphasia.

[6] The classification of aphasia into several varieties not only reflects the preconceived theories of language and aphasia (1), but also embodies the basic difficulties and epistemological problems implied in classifications at large. Nevertheless, even the uninformed interviewer can hardly escape the impression that there remains a difference between individuals unable to form words and those unable to understand spoken language, to use syntactically organized sentence structures, to repeat after the examiner or to name objects, though some, if not all of these defects, may be found side by side in the same individual at a given stage of his aphasia. Classifications, however, do not serve the purpose to reveal the inner structure or dynamics at work in an individual case; they are intended to systematize rather than to portray or to analyze nature.

REFERENCES

1. Bay, E. Theorie und Empirie bei der Klassifikation und den Untersuchungsmethoden der aphasischen Störungen. Psychiat. et neurol., **134**: 298–310, 1957.
2. Goldstein, K. *The Organism*. The American Book Co., New York, 1939.
3. Goldstein, K. *Language and Language Disturbances*. Grune & Stratton, New York, 1948.
4. Goldstein, K. The effect of brain damage on the personality. Psychiatry, **15**: 245–260, 1952.
5. Head, H. *Aphasia and Kindred Disorders of Speech*. Cambridge Univ. Press, London, 1926.
6. Riese, W. Semantic aphasia. A clinical neuro-

pathological study including a report of the first known case of semantic aphasia with complete examination of the brain. J. Nerv. & Ment. Dis., **123**: 18–22, 1956.

7. Riese, W. Frühe Fassungen und allgemeine Bedeutung der Diaschisis. Lecture delivered to the Zurich Psychiatric-Neurological Society, September 1, 1957; English version: The principle of diaschisis, its history, its nature, and its general significance. Internat. Rec. Med., **171**: 73–82, 1958.
8. Riese, W. Das Momentum der Hirnläsionen (Eine Nachuntersuchung). To be published in Schweiz. Arch. Neurol. u. Psychiat.

RUPTURED ANEURYSMS OF THE ANTERIOR COMMUNICATING ARTERY[1]

ASAO HIRANO, M.D.,[2] ROBERT D. TERRY, M.D. AND H. M. ZIMMERMAN, M.D.

INTRODUCTION

Aneurysms in the region of the anterior communicating artery have long been recognized, and have been documented in considerable numbers. Walton (15) lists 416 cases which he collected from the literature. These comprise 22 per cent of the intracranial aneurysms in his series. However, the reports are scant with regard to the details of the pathologic effects of rupture of these aneurysms. Within recent years, ten such cases have been studied at Montefiore Hospital, and analysis of this material has revealed three distinct pathologic groups. The first is characterized by massive bleeding into the subarachnoid space, without penetration of brain tissue. The second group is made up of four patients in whom the hemorrhage ruptured through the ventral or median aspect of the frontal lobe into the rostral horn of the lateral ventricle. The third group revealed bleeding into the epicallosal sulcus and necrosis of the corpus callosum with consequent rupture and hemorrhage into the bodies of the lateral ventricles. These differences in pathology are reflected by symptomatic and radiologic distinctions which may be of value to the clinician with regard to diagnosis and therapy.

CASE REPORTS

GROUP 1

Case 1: (M.H. 96436) This 64 year old hypertensive woman awoke with a severe headache 19 hours prior to admission and became increasingly stuporous. The past history was unremarkable save for an episode of syncope ten years previously. Examination revealed evidence of severe meningeal irritation and bilateral Babinski signs, but no focal signs. The spinal fluid, obtained by lumbar puncture, was grossly bloody and under increased pressure. An aneurysm of the anterior communicating artery was demonstrated by both right and left carotid angiography. The anterior cerebral arteries were not displaced. On the third hospital day anisocoria and right sided hyperreflexia appeared. A second left carotid angiogram did not reveal an intracerebral hematoma. The focal signs were considered to be due to pontine hemorrhage and surgery was not attempted. The patient expired on the ninth day of her disease.

Postmortem examination: The general autopsy findings were not significant. Increased intracranial pressure was manifested by diffuse flattening of the cerebral gyri and by uncal and tonsillar herniations. The arteries formed a complete circle of Willis, were thin-walled and marked by only occasional atheromata. Arising from the junction of the left anterior cerebral artery and the anterior communicating artery was a 6 mm. aneurysmal sac which had a thin wall and projected rostro-dorsally. The point of rupture measured about 1 mm. and was found at the apex. There was massive subarachnoid hemorrhage at the base of the brain which spread over the convexities. In the tegmentum of the pons were numerous recent hemorrhages. The ventricular system was normally disposed and free of blood except for a minimal amount in the fourth ventricle.

Case 2: (M.H. 86097) This 45 year old hypertensive woman was well until eight days prior to her death. The first symptom

[1] The Henry and Lucy Moses Research Laboratories of the Laboratory Division, Montefiore Hospital, New York City.

[2] Trainee of the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Services.

was bitemporal pressure, followed by dizziness, nausea and vomiting. The headache became severe and a stiff neck developed. On admission to the hospital the patient was comatose, had blurred optic discs and bilateral Babinski signs. The only focal finding was that of a right sixth nerve palsy. Right carotid angiography demonstrated an aneurysm of the anterior communicating artery. The anterior cerebral arteries were not displaced. The right common carotid artery was ligated, but the patient expired a few hours later.

Postmortem examination: The findings were essentially similar to those of Case 1. A 7 mm. oval aneurysm was found at the juncture of the right anterior cerebral artery and the anterior communicating artery. The long axis of the sac was directed dorsoventrally with the point of rupture on the ventral aspect. Again there was extensive subarachnoid hemorrhage without penetration of the brain tissue.

Case 3: (M.H. 51167) This 48 year old hypertensive woman suddenly developed a headache followed by nausea and vomiting. One hour later she became comatose and had occasional tonic convulsions. The past history was unremarkable. There were nuchal rigidity and bilateral Babinski signs, but no focal neurologic findings. At lumbar puncture the spinal fluid had an initial pressure of 290 mm. of water and was grossly bloody. The patient expired after a total course of only 27 hours.

Postmortem examination: The findings were similar to those of the first two cases. The massive subarachnoid hemorrhage (Figure 1) was caused by the apical rupture of a 5 mm. aneurysm directed rostrally from its origin at the junction of the anterior communicating artery and the left anterior cerebral artery.

GROUP 2

Case 4: (M.H. 47,922) This 48 year old hypertensive man was admitted complaining of severe headache which had come on suddenly and was followed by dizziness and vomiting. The patient had been hospitalized elsewhere seven years previously for subarachnoid hemorrhage. There had been no residual neurologic deficit, but at least six times during the following years he had had severe headache and stiff neck. On each occasion he was treated with prolonged bed rest at home. Examination five hours after the onset of the present episode revealed mental confusion, lethargy and nuchal rigidity. The spinal fluid was grossly bloody and was under increased pressure. There was gradual clinical improvement until the sixth hospital day when he suddenly developed a generalized seizure. At lumbar puncture the opening pressure was 440 mm. of water, and the spinal fluid contained much fresh blood. An electroencephalogram showed diffuse delta wave activity, most prominent in the left frontal region. Left carotid angiography failed to opacify the anterior cerebral artery, nor did it demonstrate an aneurysm. The patient's condition continued poor and he died on the ninth hospital day.

Postmortem examination: The general autopsy findings were not significant. The cranial leptomeninges contained only a small amount of blood. The cerebral gyri were flattened, while the unci and cerebellar tonsils were herniated. The vessels at the base of the brain were moderately arteriosclerotic but the lumens were everywhere patent. A thrombosed, 1 cm. aneurysm was found at the junction of the left anterior cerebral artery and the anterior communicating artery. The sac invaginated the medial surface of the left gyrus rectus and a hemorrhagic tract penetrated the left frontal lobe from this point. The left forceps minor of the corpus callosum was ruptured, and the left lateral ventricle was filled with blood which displaced the septum pellucidum. The third and fourth ventricles also were filled with blood. There were a few small pontine hemorrhages.

Case 5: (M.H. 57789) This 60 year old

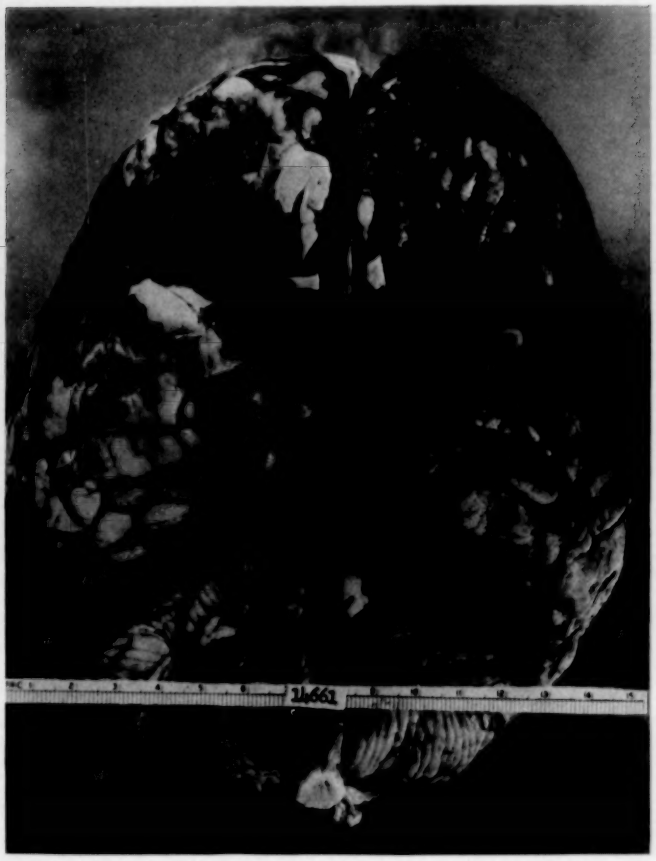

FIG. 1. Case 3. (M.H. 51167; Autopsy No. 14661). Massive subarachnoid hemorrhage at base of brain. The aneurysm, which was situated at the junction of the anterior communicating and the left anterior cerebral artery, is covered with blood and is not visible.

hypertensive woman had had a "stroke" without sequellae nine years before the present episode. On the day of admission she struck her head on a cabinet and began to complain of headache. Five hours later she was found unconscious. She was brought to the hospital in coma with large hemorrhages in the right fundus and with bilateral Babinski signs. The neck was supple and Kernig signs were not elicited. Immediate craniotomy was performed but the expected subdural hematoma was not found. The patient died in the operating room.

Postmortem examination: There was only slight subarachnoid hemorrhage. At the junction of the left anterior cerebral artery and the anterior communicating artery was a ruptured, spherical, 7 mm. aneurysm. A hemorrhagic tract (Figure 2) penetrated the subcallosal gyrus, through the rostrum, into the blood-filled rostral horn of the left lateral ventricle. The septum pellucidum was ruptured so that the right lateral ventricle as well as the third and fourth ventricles was also filled with blood. A single hemorrhage was noted in the pons.

Case 6: (M.H. 95160) This was a 65 year old hypertensive who noted a severe headache on the morning of her admission. In mid-afternoon she suddenly cried out and

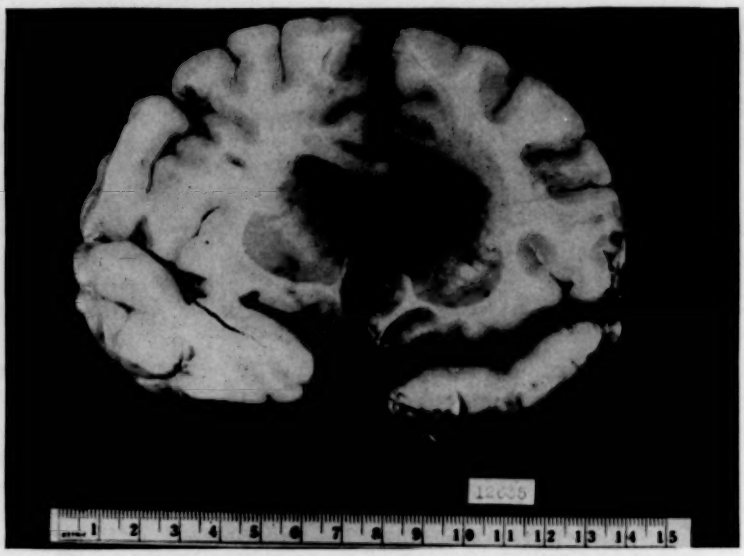

FIG. 2. Case 5. (M.H. 57789; Autopsy No. 12635). Both anterior horns are filled with blood; the septum pellucidum is torn. Below the brain slice there is the aneurysm at the junction of the left anterior cerebral and the anterior communicating artery.

then lost consciousness. The waking state was regained after 15 minutes, but the patient was confused and complained of nausea. The past history was not obtainable. Examination revealed right central facial weakness and questionable nuchal rigidity. The spinal fluid was very bloody and its pressure was recorded as 300 mm. of water. The patient expired the same day, before further procedures could be undertaken.

Postmortem examination: There was moderate subarachnoid bleeding. A 5 mm., ovoid aneurysm was found at the junction of the left anterior cerebral artery and the anterior communicating artery. The sac was ruptured at its rostral apex and a hemorrhagic tract extended through the medial portion of the frontal lobe and through the left forceps minor. The entire ventricular system was filled with a cast of blood. At the level of the anterior tip of the caudate nucleus, the tract was continuous with a 2 cm. hematoma located ventral to the rostral ventricular horn which was displaced dorsally.

Case 7: (M.H. 39683) This 44 year old woman suffered the sudden onset of headache and vomiting. On admission 12 hours later nuchal rigidity and left hemiparesis were found. About one hour after admission she had a generalized tonic-clonic seizure and lapsed into deep coma. The spinal fluid was grossly bloody. The patient died 30 hours after the onset of symptoms.

Postmortem examination: A ruptured aneurysm was found at the junction of the right anterior cerebral artery and the anterior communicating artery. The gyrus subcallosus and rostrum of the corpus callosum were partially destroyed by the hemorrhage. Blood filled the entire ventricular system.

GROUP 3

Case 8: (M.H. 100763) This 68 year old woman was found unconscious in bed and entered the hospital in coma. She did not have a history of hypertension or of headaches. The blood pressure was 100/70 and respiration was of the Cheyne-Stokes vari-

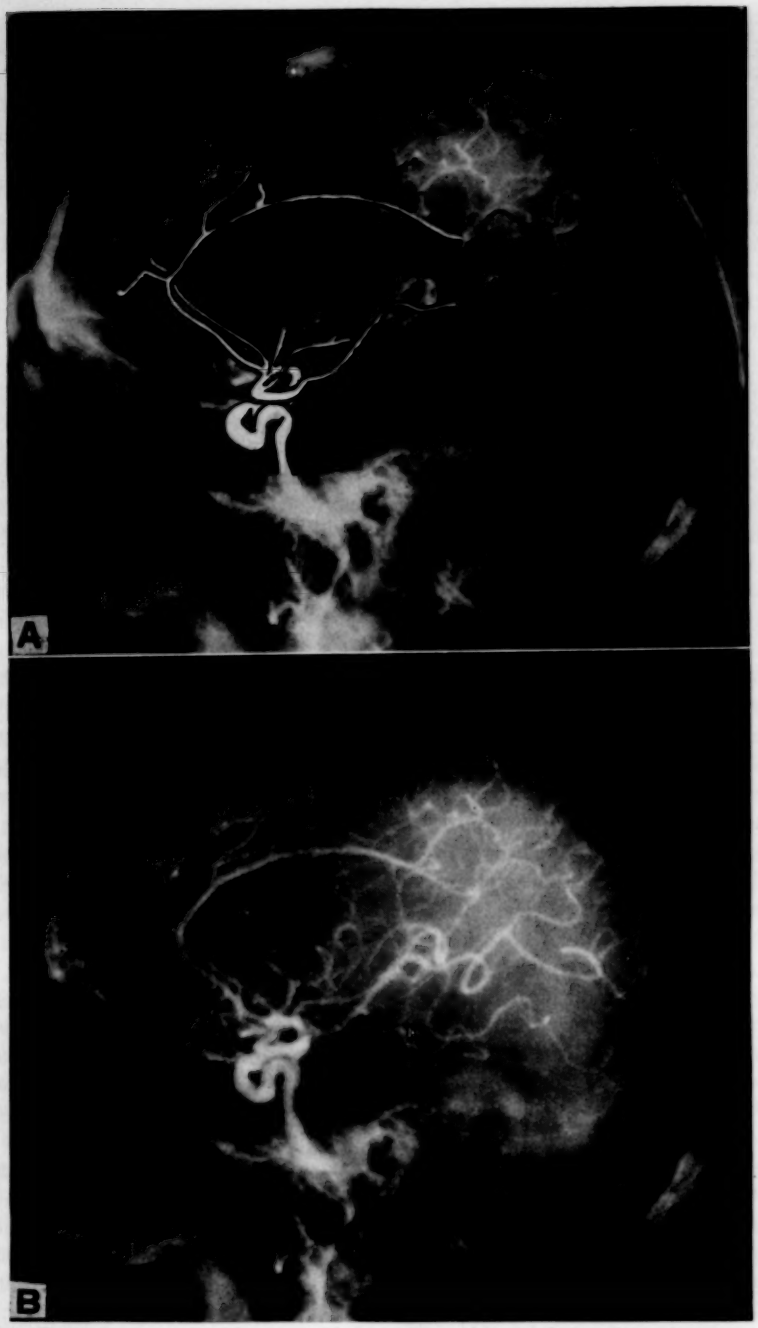

FIG. 3A and B. Case 8. (M.H. 100763; Autopsy No. 15290). Right carotid angiogram. Both anterior cerebral arteries are visualized, stretched and displaced upwards as is seen with internal hydrocephalus. The carotid siphon is compressed, but the aneurysm is not delineated.

ety. Neurologic examination did not reveal focal signs. The neck was supple, and the pupils were equal and reacted to light. The fundi were normal. Bilateral Babinski signs were observed. Lumbar puncture showed bloody spinal fluid with a pressure of 110 mm. of water. Bilateral carotid angiography was performed on the night of admission. Injection of the right carotid (Figure 3A and B) opacified both anterior cerebral arteries which were stretched and displaced upwards as if by internal hydrocephalus. A round, aneurysm-like shadow on the anterior communicating artery was noted only in the anterior-posterior view. The left carotid injection opacified the left anterior and middle cerebral arteries but did not demonstrate an aneurysm. Surgical therapy was withheld due to the lack of definitive localization and slow improvement in the state of consciousness. The patient expired suddenly three days after the onset of symptoms.

Postmortem examination: The autopsy was limited to study of the brain and spinal cord. A small amount of subarachnoid blood was noted over the orbital gyri and in the basal cistern. There was also a thin film in the Sylvian fissures and over the cerebellum. Increased intracranial pressure was manifested by flattened cerebral gyri and bilateral uncal herniation. The right cingulate gyrus bulged toward the midline. The circle of Willis was complete and the arteries, although sclerotic, were patent. A 3 x 4 mm. aneurysm arose from the anterior communicating artery and involved both anterior cerebral arteries, more especially that on the left. The point of rupture was a minute defect at the rostro-dorsal apex of the sac.

Coronal sections revealed a mass of blood in the sulcus of the corpus callosum, elevating both pericallosal arteries and depressing the corpus callosum. The body of the latter structure was focally necrotic and disrupted. Blood filled the ventricular system and presented at the foramina of Luschka. The supracallosal hemorrhage extended laterally into the white matter of the frontal lobes and partially destroyed the cingulate gyri. The lateral ventricles were flattened from above. The lamina terminalis was found buried by the blood in the third ventricle and in the basal cistern.

Case 9: (M.H. 89299) This 49 year old hypertensive man was well until eight days before admission to Montefiore Hospital. At that time he suddenly fell unconscious and was brought to another hospital where the spinal fluid was found to be bloody and under increased pressure. A left carotid angiogram demonstrated an aneurysm of the anterior communicating artery. The patient's condition deteriorated and he was transferred to Montefiore Hospital. On admission he was somnolent and complaining of headache. The blood pressure was 200/80. Nuchal rigidity and a positive Kernig sign were present but lateralizing signs were not found. The optic discs were blurred and there were multiple retinal hemorrhages. The tendon reflexes were hyperactive but abnormal reflexes could not be elicited. At lumbar puncture the initial pressure was 400 mm. of water. The spinal fluid was deeply xanthochromic but contained only a few red blood cells. On the day after admission, bilateral carotid angiography demonstrated an aneurysm of the anterior communicating artery. The sac filled from both sides. The patient's condition improved steadily during the next 13 days. On the 22nd day after the onset, a bifrontal craniotomy was performed. A 1 cm. bilobed aneurysm partly buried in the right frontal lobe was identified. Two winged Olivecrona clips were placed across the base of the sac so that neither the anterior cerebrals nor the anterior communicating artery was occluded. Following operation the patient responded to painful stimuli and gradually became more alert. On the 12th postoperative day he suddenly lost consciousness and died 40 minutes later.

Postmortem examination: The autopsy was limited to removal of the brain. The

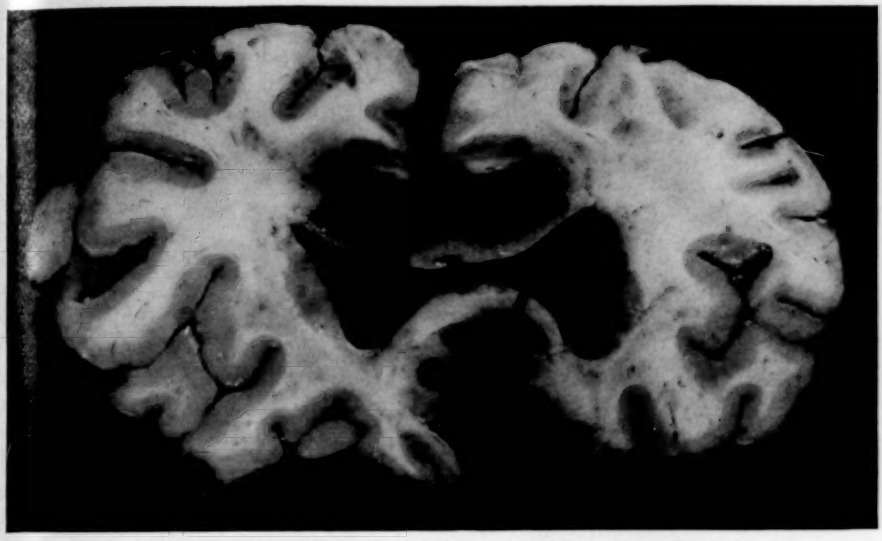

FIG. 4. Epicallosal hemorrhage with necrosis of the corpus callosum.

sagittal sinus was found to be ligated anteriorly but the vessel was otherwise patent. A thin film of subarachnoid blood covered the frontal poles, the optic chiasm and the cerebellum. The circle of Willis was complete and was essentially free of atherosclerosis. A 5 x 2 mm. aneurysm was located at the junction of the anterior communicating artery and the left anterior cerebral artery. Two surgical clips occluded the base of the sac which was ruptured at its apex. There was, however, another perforation immediately proximal to the more medial clip. Coronal sections of the cerebrum demonstrated an extensive hemorrhage (Figure 4) in the sulcus of the corpus callosum and extending laterally into the frontal white matter. The pericallosal arteries were elevated above the blood clot and the corpus callosum was depressed. Hemorrhagic softening was noted in the corpus callosum at the level of the mammillary bodies. Blood filled the ventricular system.

Case 10: (M.H. 51247) This 50 year old woman entered the hospital because she had had two grand mal seizures during the previous two months. On admission she was alert and cooperative with a blood pressure of 170/88. There were no constant focal neurologic signs but the electroencephalogram showed a diffuse slow pattern in the theta range, most prominent in the frontal region. Pneumoencephalography demonstrated what was thought to be a 3 cm. mass pushing down the roof of the frontal horns. At craniotomy yellow material was noted on the dorsal surface of the anterior portion of the corpus callosum. Tumor was not found. Histologic preparations of the biopsy showed it to be cerebral tissue containing hemosiderin laden macrophages and reactive gliosis. The patient did not recover consciousness and died two days postoperatively.

Postmortem examination: The general autopsy findings were not significant. Gyral flattening, slight uncal herniation and tonsillar coning indicated mildly increased intracranial pressure. The right first frontal gyrus, in the area of surgical manipulation, was marked by hemorrhagic infarction. A thin film of old subarachnoid blood pigment was noted at the base and over the cerebellum. A 1.5 cm. thrombosed aneurysm was

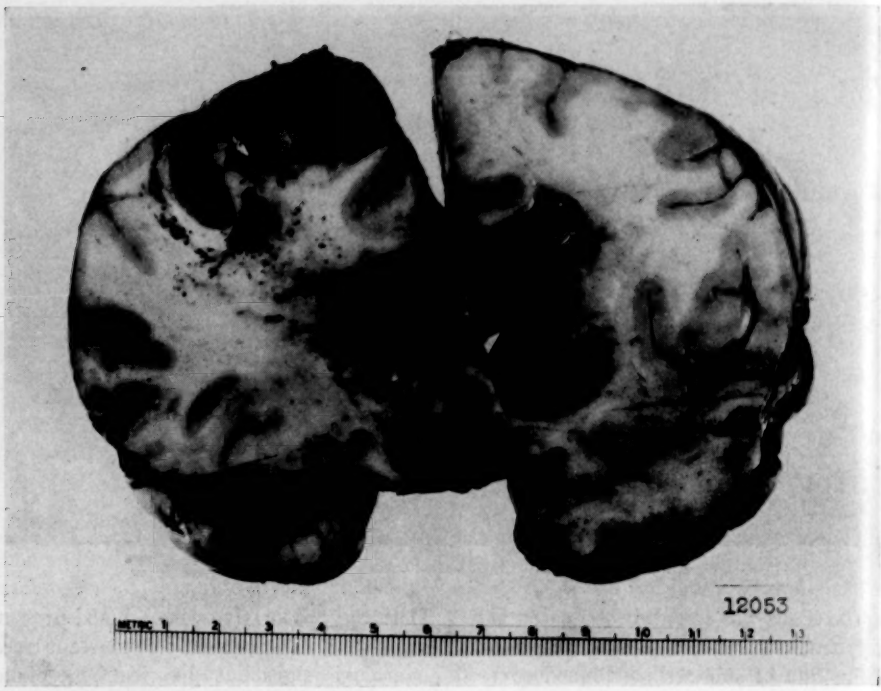

FIG. 5. Case 10. Epicallosal hemorrhage has flattened the lateral ventricles. Severe necrosis of the corpus callosum is apparent. The hemorrhage in the first frontal gyrus corresponds with the area of surgical manipulation.

located at the junction of the anterior communicating artery and the left anterior cerebral artery. The sac extended across the midline and was partially buried in the right rectal gyrus. Both pericallosal arteries were occluded by clot of the same appearance as that which filled the aneurysm. These vessels were separated from the corpus callosum by hemorrhage (Figure 5) which was adherent to the cingulate gyrus and had penetrated the adjacent centrum ovale by way of the sulcus of the corpus callosum. The lateral ventricles were flattened downward by the depressed and necrotic corpus callosum. A small amount of fresh blood was present in each ventricle.

DISCUSSION

These ten patients ranged in age from 44 to 68 years. The intracerebral vessels were not severely arteriosclerotic, nor were the aneurysms themselves. A small atheromatous plaque was commonly found near the sac, but a causal relationship between arteriosclerosis and aneurysm formation was never demonstrated. The circle of Willis was symmetrical and free of gross anomalies in all 10 cases. Congenital anomalies were not found in other organs and in no instance was there evidence of polycystic renal disease.

The aneurysms were all solitary, and none was larger than 15 mm. in greatest diameter. Particularly noteworthy was the finding that in every instance the aneurysm involved both the anterior communicating artery and the adjacent anterior cerebral artery. The sacs were more sessile than is generally appreciated, so that in taking origin from the angle, the neck arose from both vessels. This width is similar to that noted by Hamby (6), and may well account for

some of the difficulties encountered in attempts to clip this type of sac at its base. The predominance of left sided origin of the aneurysms in this small series is statistically insignificant.

The aneurysms were directed rostrally and dorsally with the point of rupture in each case near the apex. In no case was the optic nerve or chiasm compressed by the sac although visual field defects due to compression of optic nerves and chiasm by unruptured, large aneurysms have been reported (4, 7, 9, 14).

Group 1: All cases of this type presented

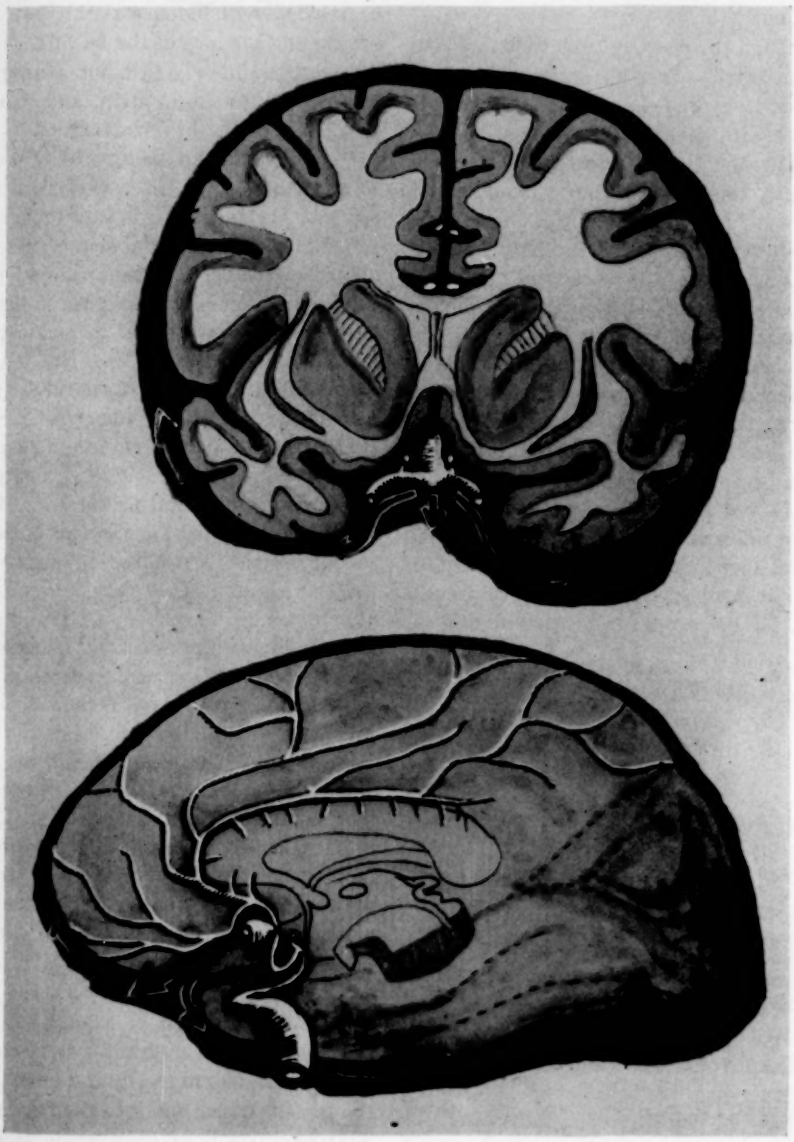

FIG. 6. Drawing of Type 1 illustrating subarachnoid hemorrhage.

clinical evidence of increased intracranial pressure without significant lateralizing signs. The unilateral abducens paralysis in Case 2 is indicative only of this hypertension. The preterminal right hyperreflexia of Case 3 is to be explained by the pontine hemorrhage (related to supratentorial pressure) and again was not a symptom of cerebral damage.

Although the onset in each case was sudden, there was never an immediate loss of consciousness. The course was steadily progressive without evidence of improvement. Courville and Olsen's cases 2, 3 and 5 (1) exemplify this type of subarachnoid hemorrhage with rapid, fatal course. Robertson's (11) survey of ruptured aneurysms indicated that death in the first day of disease was more common with pure subarachnoid hemorrhage, while those patients with intracerebral hematomas more often died in the second week. It is undoubtedly true, however, that not all patients with hemorrhage localized in the subarachnoid space die in the first attack. Courville's (1) cases 14 and 18 suffered recurrent episodes. Dandy (3) wrote that in the case of intracerebral bleeding, the hemostatic effect of the adjacent tissue may help prevent early death. Of the seven such cases in this series, five (numbers 4, 5, 8, 9 and 10) had definite clinical evidence of repeated attacks.

TABLE 1

Summary of Observations Discussed in Text

	Group		
	1	2	3
Number of cases	3	4	3
Subarachnoid blood	++++	+	+
Blood in epicallosal sulcus	0	0	++
Intraventricular blood	0	++	++
Site of ventricular rupture	0	gyrus subcallosus and minor forceps	body of corpus callosum
Pericallosal arteries	normal	normal	elevated
Lateral ventricles	normal	unilateral dilatation	flattened

Nuchal rigidity and bilateral Kernig signs were present in each case, attesting to the meningeal irritation due to the extensive subarachnoid hemorrhage which is characteristic of this group. At autopsy (Figure 6) the layer of blood was thickest on the orbital surface and in the basal cisterns. It extended to the Sylvian fissures, around the cerebellum and brain stem, and was thinnest over the cerebral convexities.

Group 2: Prior to the reports by Wallesch (13), Courville and Olsen (1) and Richardson and Hyland (10), it was thought that rupture of an intracranial aneurysm resulted almost exclusively in hemorrhage localized to the subarachnoid space. There had been only rare case reports of intracerebral hematomas due to aneurysms. But twelve of Courville's 17 cases (1) of ruptured anterior communicating artery aneurysm, seven of Richardson's (10) nine cases and 29 of Robertson's (11) 34 cases in this location resulted in intracerebral hemorrhage. Walton (15) had 26 ruptured aneurysms of this vessel, of which 18 resulted in intracerebral hemorrhage and eight simply in subarachnoid bleeding. Seven of the ten cases reported here were similarly affected. The cumulative incidence of intracerebral hematoma for these four series is thus 76 per cent. Meadows (8) further emphasized the importance of intracerebral hemorrhage.

In those cases marked by intracerebral and intraventricular hemorrhage, there is often relatively little blood in the subarachnoid space (Table 1). Meningeal irritation may be absent in these patients. Nuchal rigidity was not found in four of the seven patients in Groups 2 and 3.

The major lesion of Group 2 is the hemorrhagic tract (Figure 7) extending through the gyrus rectus or gyrus subcallosus into the white matter of the frontal lobe, through the forceps minor and into the frontal horn. This has also been illustrated by Hamby

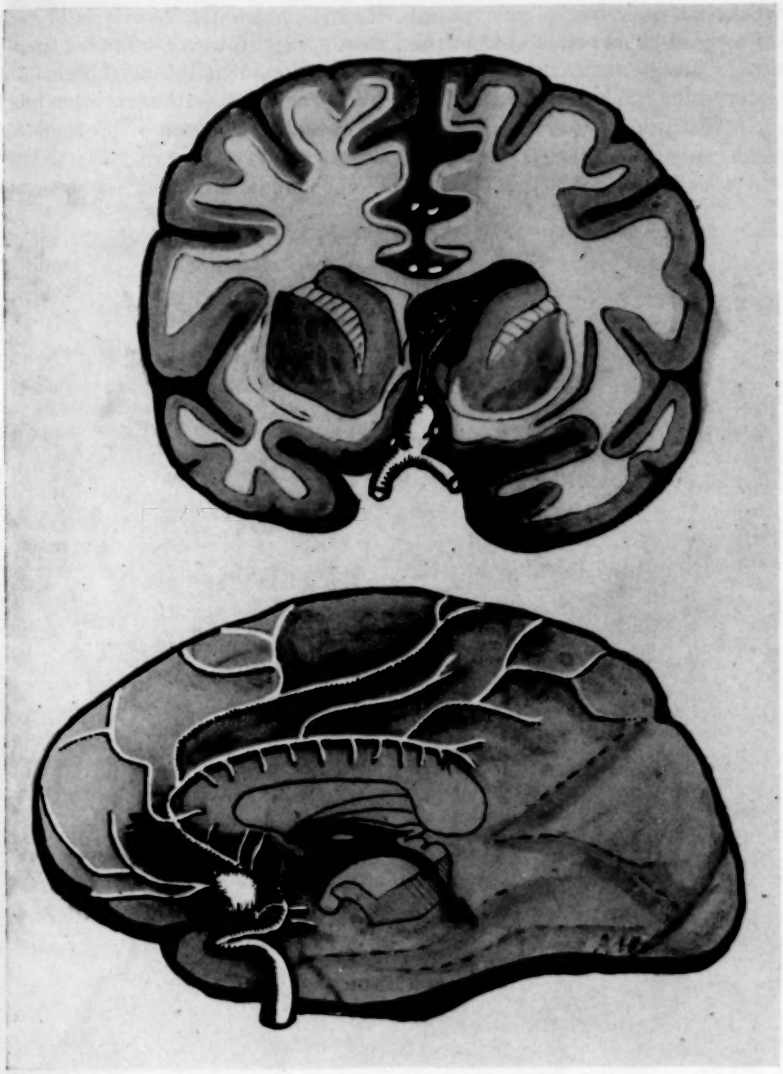

FIG. 7. Drawing of Type 2 showing hemorrhagic rupture of the rostrum of the corpus callosum with intraventricular bleeding.

(6). The anterior portion of one ventricle is dilated as in Cases 4, 5 and 6. A cast of blood extends through the third and fourth ventricles and may present at the foramens of Luschka. Intracerebral hematoma ventral to the frontal horn but without ventricular rupture has been mentioned in the literature.

The pathogenesis of these Group 2 lesions is obscure. Echols and Kirgis (5) have reported a case in which an unruptured, pedunculated aneurysm penetrated the frontal lobe to lie within the ventricle. Zimmerman (16) described a similar aneurysm which lay adjacent to the ventricle and ruptured into it. But much more common are the ex-

ternal aneurysms described in this series. The jet of arterial blood escaping from the ruptured sac might be sufficiently strong to tear the intervening cerebral tissue. Another possibility is that prior occlusion or tearing of the small penetrating vessels supplying the orbital area might produce an infarct through which the blood could penetrate more easily. However, infarcted tissue is not usually found in the neighborhood of the tract. Furthermore, there is often no clinical or histologic evidence of previous bleeding episodes.

The lamina terminalis has been suggested

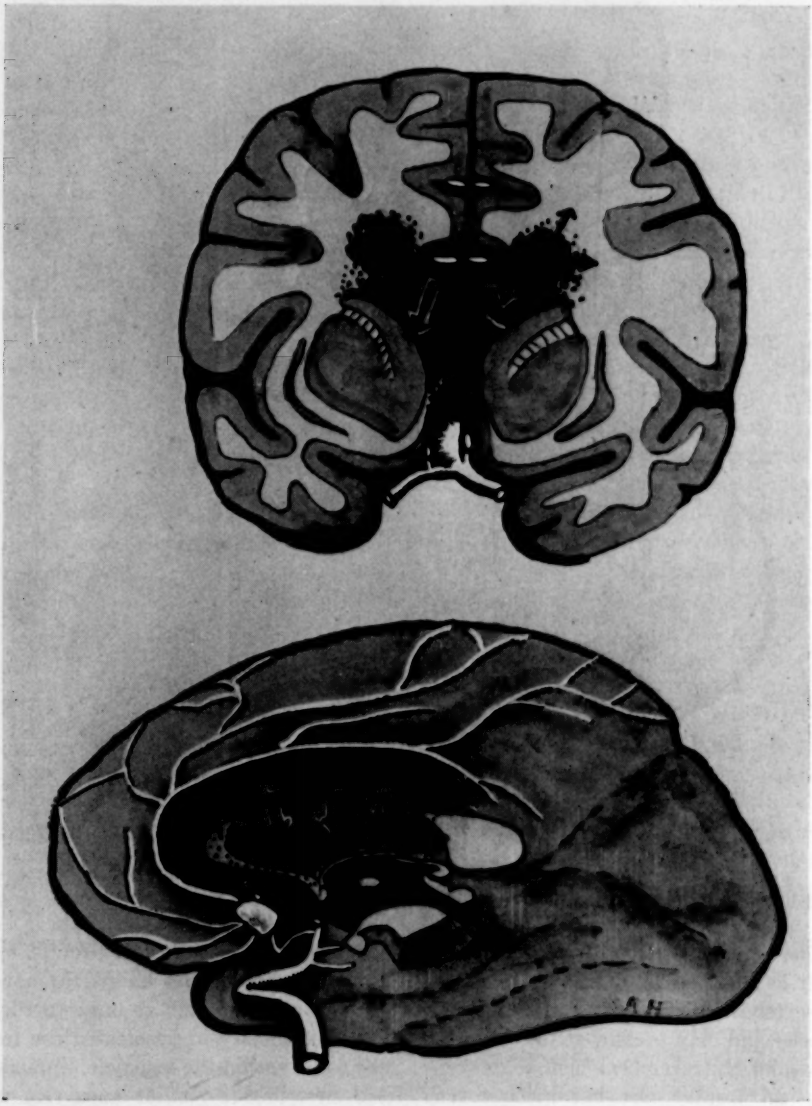

FIG. 8. Drawing of Type 3 demonstrating the epicallosal hemorrhage with elevation of the pericallosal arteries. The corpus callosum is depressed and necrotic. The ventricles are flattened and blood-filled.

(Courville and Olsen (1) and Robertson (11)) as an occasional site of rupture into the ventricular system. In this series, this membrane lay deeply buried in the clot which filled the chiasmatic cistern and the third ventricle. In no case could a rupture be demonstrated.

Group 3: This type of lesion has not previously been clearly described although the 17th case of Courville (1) may be of this kind. Walton's case No. 273 (15) may also belong to this group. Characteristic is the massive supracallosal hemorrhage (Figure 8) spreading bilaterally through the epicallosal sulci into the frontal white matter. The body of the corpus callosum is pushed ventrally and is infarcted and ruptured. The lateral ventricles are symmetrically compressed from above and the ventricular system is filled with blood. The anterior cerebral and pericallosal arteries are elevated above the hemorrhage with consequent tearing of the perforating branches which supply the corpus callosum. This apparently accounts for the callosal necrosis and rupture. Those branches which supply the mesial surfaces of the posterior frontal lobe are, however, intact. Thus there are no signs of paresis of the lower extremity such as Critchley (2) described in occlusion of the anterior cerebral artery. The stretching and elevation of these vessels causes an arteriographic image which may be easily confused with internal hydrocephalus.

Sweet (12) has also described callosal necrosis in a patient with a seeping aneurysm of the anterior cerebral artery. In his case there was no blood dorsal to the corpus callosum and the necrosis in that case must be due to causes other than tearing of the perforating vessels.

Many neuropathology laboratories utilize horizontal sections for gross dissection of the brain at autopsy. Supracallosal hemorrhage of the type emphasized in this report is poorly visualized by this method. Coronal brain sections are much to be preferred in cases of ruptured aneurysm of the anterior communicating artery.

SUMMARY

Three pathologic groups are delineated in ten patients with ruptured aneurysms of the anterior communicating artery. The first group has massive subarachnoid bleeding without cerebral disruption. The second group is marked by less subarachnoid hemorrhage but with rupture through the forceps minor into the ventricles from below. The third group is characterized by a butterfly-shaped hematoma dorsal to the corpus callosum which is depressed and perforated.

REFERENCES

1. Courville, C. B. and Olsen, C. W. Miliary aneurysm of anterior communicating artery; clinical and pathological report of 19 cases, 18 with fatal hemorrhage. Bull. Los Angeles Neurol. Soc., **3**: 1–21, 1938.
2. Critchley, M. The anterior cerebral artery and its syndromes. Brain, **53**: 120–165, 1930.
3. Dandy, W. E. *Intracranial Arterial Aneurysms.* Comstock Publishing Co., Ithaca, 1944.
4. Duke-Elder, W. S. *Textbook of Ophthalmology*, Vol. 4. C. V. Mosby, Co., St. Louis, 1949.
5. Echols, D. H. and Kirgis, H. D. Intraventricular extension of an aneurysm of the anterior cerebral artery. Surgery, **27**: 260–267, 1950.
6. Hamby, W. B. *Intracranial Aneurysms.* Charles C Thomas Co., Springfield, Ill., 1952.
7. Jefferson, G. Compression of the chiasma, optic nerves and optic tracts by intracranial aneurysms. Brain, **60**: 444–497, 1937.
8. Meadows, S. P. Intracranial aneurysms. In *Modern Trends in Neurology*, Feiling, A., ed., pp. 391–465. Paul B. Hoeber, Inc., New York, 1951.
9. Moore, M. T. and Bockman, A. A. Ruptured aneurysm of left anterior cerebral artery with production of ipsilateral cerebral signs. Arch. Neurol. & Psychiat., **46**: 1057–1067, 1941.
10. Richardson, J. C. and Hyland, H. H. Intracranial aneurysms: clinical and pathological study of subarachnoid and intracerebral hemorrhage caused by berry aneurysms. Medicine. **20**: 1–83, 1941.
11. Robertson, E. G. Cerebral lesions due to intracranial aneurysms. Brain, **72**: 150–185, 1949.

12. Sweet, W. H. Seeping intracranial aneurysm simulating neoplasm. Syndrome of corpus callosum. Arch. Neurol. & Psychiat., **45**: 86–104, 1941.
13. Wallesch, E. Die Verlaufstypen der Rupturaneurysmen am Hirngrube. Virchows Arch. path. Anat., **251**: 107–136, 1924.
14. Walsh, F. B. *Clinical Ophthalmology*, 2nd ed. Williams and Wilkins Co., Baltimore, 1957.
15. Walton, J. N. *Subarachnoid Haemorrhage*. E. S. Livingstone Ltd., Edinburgh, 1956.
16. Zimmerman, H. M. Cerebral apoplexy: mechanisms and differential diagnosis. New York J. Med., **49**: 2153–2157, 1949.

ENDOCRINE AND METABOLIC CONDITIONS RELATED TO PATHOLOGY IN THE HYPOTHALAMUS: A REVIEW

HANS G. BAUER, M.D.[1]

INTRODUCTION

The investigation of human neuro-endocrine control is still in its infancy despite vast amounts of pertinent information obtained by animal experimentation. This is partly due to understandable difficulties of approach. Admittedly recent technologic advance in the field of electronics has made it possible to furnish electroencephalographic information from human subcortical centers without major surgical interference. The great potential of this type of research is fully appreciated. However, it is clear that the analysis of clinical manifestations in patients with brain pathology, carried out against the background of animal research, is also most desirable.

In this paper a series of 100 patients with cerebral lesions, verified by autopsy, have been studied as to their clinical symptoms and the corresponding autopsy findings, especially in regard to pathology of the hypothalamus and related centers. Sixty patients with hypothalamic pathology, reported in a previous publication (4), have been included. Special emphasis will be given to water metabolism in conjunction with some aspects of electrolyte control, and the regulation of gonadal, adreno-cortical and thyroid secretions. The latter three topics will be discussed mainly in regard to the release of the respective trophic hormones. Pertinent topics relating to information gained by animal research will be discussed.

The topography of hypothalamic centers is illustrated in Figures 1–3. Table 1 presents the key to these figures.

ANATOMIC FACTORS IN HYPOTHALAMIC DISEASE

The hypothalamus is found in the walls and the floor of the third ventricle. It contains approximately 15 identifiable nuclear centers. Some of these lie close to the ependymal lining of the walls of the ventricle, such as the periventricular, paraventricular, the ventral and dorsomedial nuclei. Numerous openings in this ependymal lining permit the passage of neural transmitting agents such as adrenaline-like substances and acetylcholine, as well as other hormones. A slight increase in pressure of the cerebrospinal fluid may interfere with these exchanges, even to the point of causing bilateral atrophy of the adjacent medial nuclear centers. Heinbecker (23) has described four cases where such changes could be demonstrated. He reported atrophy of the ependymal lining as well as of the paraventricular nuclei in these subjects. Typical Crooke cell changes could be demonstrated in the anterior lobe of the pituitary. Furthermore, these patients displayed typical features of Cushing's syndrome. None of the other conditions known to cause this syndrome could be demonstrated at autopsy.

In order to alter the function of hypothalamic centers, nearly all investigators have emphasized the importance of establishing bilateral lesions in the paired centers of the diencephalon. This fact is helpful in our clinical and diagnostic considerations of hypothalamic lesions in human beings.

The lower part of the anterior wall of the third ventricle is formed by the optic chiasm. Therefore, bitemporal or simple temporal field defects are frequently associated with pathology in the third ventricle. The optic

[1] The Intermediate Service of the Veterans Administration Center, Martinsburg, West Virginia. This paper was presented in part at the Fifth International Congress of Internal Medicine, Philadelphia, April, 1958. The author wishes to thank Dr. Thomas H. McGavack for suggestions in its preparation.

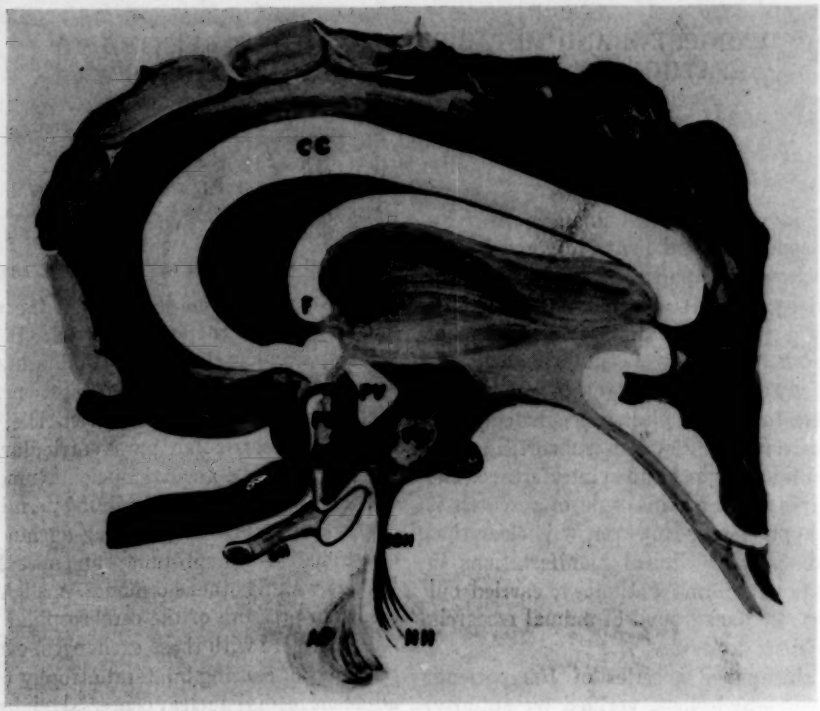

FIG. 1. Median sagittal section through the cerebral hemisphere, showing location of hypothalamic nuclei.

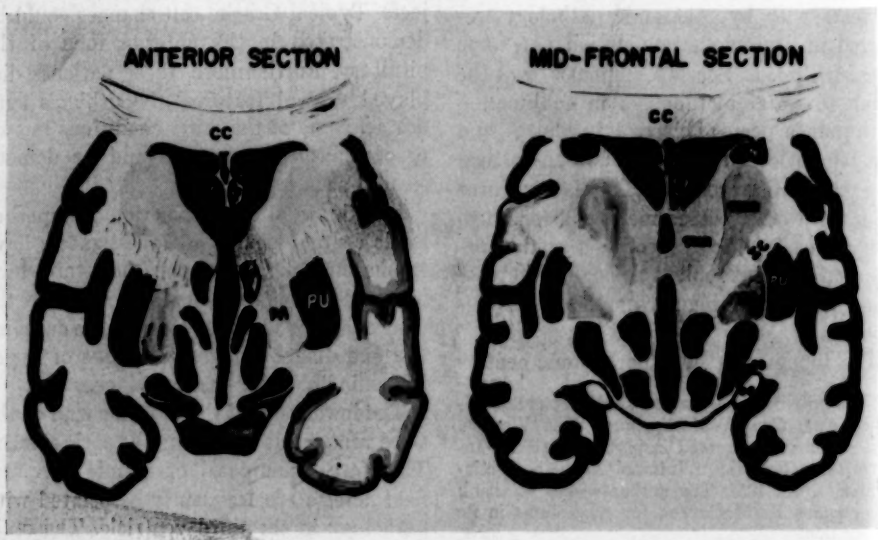

FIG. 2. Hypothalamic nuclei: anterior section and mid-frontal section

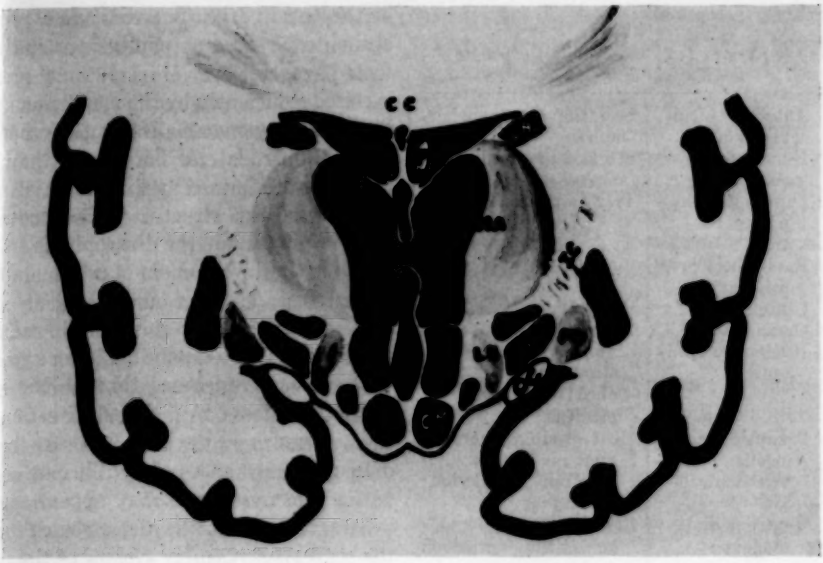

FIG. 3. Hypothalamic nuclei: posterior frontal section.

tracts run next to the walls of the ventricle. When pressure is exerted on either of these tracts *via* expanding third ventricle lesions homonymous hemianopsia often follows. Both types of hemianopsia are often preceded by central scotomata. In the group of 60 cases with hypothalamic pathology, nine patients had homonymous and nine had temporal hemianopsia; two of the latter were unilateral. In other words 18 patients (30 per cent of this sample) showed evidence of defects in their visual fields.

The optic nerve is another close neighbor of the anterior areas of the hypothalamus. Pressure on this nerve will lead to the appearance of central scotomata first and finally to total blindness in the affected eye. Tangent screen examination of visual fields has to be applied for the early detection of central scotomata. Furthermore, changes in pupillary reactions will be a reflection of such pressure atrophy. Other ocular nerves in the proximity of the diencephalon are the oculomotor and abducens. Injury to these by expanding lesions from the hypothalamic area will disturb the coordinated movements of the eyeballs and thus lead to strabismus. The pupillary reactions will be affected in cases with oculomotor nerve lesions. The incidence of these opthalmologic signs among the group of 60 patients was as follows: abnormal pupillary reactions in 22, papilledema in 20, optic atrophy in 14, strabismus in 11, and evidence of lesions of the oculomotor nerves in seven instances.

According to Kestenbaum (29) papilledema can only occur if the subarachnoid space accompanying the optic nerve is still communicating with the intracranial cerebrospinal fluid. Therefore, brain tumors remote from the optic nerve will tend to cause initial or more pronounced papilledema, homolateral to the location of the tumor, while tumors close to the optic nerve, *i.e.* tumors prone to produce hypothalamic dysfunction, will show homolateral optic atrophy and contralateral papilledema. The latter combination of signs is called the Foster-Kennedy syndrome, especially if homolateral anosmia is also present. For instance, a meningioma of the olfactorial groove may cause this syndrome. The pressure on the optic nerve may not permit free communication of cerebrospinal fluid in the subarachnoid space

TABLE 1

Key to Figures 1, 2, and 3, with Comments on Nuclear Functions

AP: Anterior pituitary gland	Secretion of trophic hormones
NH: Neurohypophysis	Storage of ADH principle
SOH: Supraoptico-hypophyseal tract	Transportation of ADH
PT: Pars tuberalis of pituitary	
OC: Optic chiasm	
ON: Optic nerve	
SO: Nucleus supraopticus	Secretion of ADH, stimulation of release of ADH in posterior pituitary
PO: Preoptic area	Heat dissipating center
PV: Nucleus paraventricularis	Sexual and metabolic. functions. Lesion: obesity
VM: Ventromedial nucleus	Lesions: obesity, hypogenitalism, voracious appetite, rage
DM: Dorsomedial nucleus	Lesions: hypodipsia. Stimulation polydipsia
LA: Lateral hypothalamic area or feeding centers	Stimulation: continued eating without rage and metabolic changes
CM: Corpora mamillaria	Inhibitory centers of sex stimulating tuberal centers
F: Fornix	Connects hypothalamus with cortex: hippocampus, etc.
S: Septum Pellucidum	
CC: Corpus Callosum	
ME: Median eminence	Site of neuro-humeral release (ACTH, TSH, GTH)
III V: Third ventricle	Transport of neuro-humeral, hormonal agents from systemic circulation, portal circulation
PA: Globus pallidus	
PU: Putamen	
IC: Internal capsule	
CN: Candate nucleus	
LV: Lateral ventricle	
BP: Basis pedunculi	
SN: Subthalamic nucleus	
PHA: Posterior hypothalamic area	

of the optic nerve. The result is a primary optic atrophy and no papilledema in the affected eye. However, if intracranial pressure is raised sufficiently by the meningioma papilledema may materialize in the other eye.

The upper, lateral borders of the hypothalamus are formed by the internal capsule. Pressure on this structure by expanding lesions originating in the diencephalic area resulted in the development of pyramidal tract disturbances, in 45 of our 60 patients. Pressure on the cerebral peduncles will cause the same signs. If the expanding lesions grow by way of least resistance through the interpeduncular fossa in a dorsal direction and exert pressure on the various cerebellar pedunculi, disturbances of equilibrium, coordination and nystagmus may appear.

Structures below the diencephalon include the stalk, the vascular system of the portal circulation and the pituitary gland. The portal circulation links the hypothalamus with both lobes of the pituitary gland by a fine capillary network arising from the internal carotid artery. The stalk contains numerous fine canaliculi which are in direct continuity with the infundibular process and thus, the cerebro-spinal fluid.

Through the anatomic channels just described a delicate interplay of neurohumoral and other hormonal agents is permitted (20, 21, 54–59). Aside from noradrenaline and acetylcholine probably all trophic hormones of the anterior pituitary, as well as other hormones transported *via* the blood stream are involved. In this way a fine hypothalamic adjustment of release or blockage of pituitary secretions according to the needs of peripheral glands and organ systems is accomplished. The details of these changes as well as the somewhat different behavior of anti-diuretic hormone will be further elaborated below.

From what has already been said, it is clear that a neoplasm in the hypothalamic area growing towards the pituitary gland will interfere seriously with this fluid ex-

change system, thus disturbing the hypothalamic control, even before the gland itself is reached and compressed. Syndromes very similar to pituitary pathology may thus occur, simulating dysfunction of endocrine target organs.

On the other hand a neoplasm, such as a craniopharyngeoma, may arise from epithelial remnants in the hypophyseal duct and grow in a rostral direction, thus exerting pressure first on the anterior hypothalamus. Very frequently a syndrome of hypogenitalism, obesity and diabetes insipidus plus the above mentioned eye signs results. According to the point of origin, in the upper or lower "anlage" of these tumors, *i.e.*, intra- or suprasellar, the pituitary gland will be more or less affected.

The upper border of the hypothalamus as the name implies is the thalamus. Growth extension into this organ is rare, but when occurring may cause bizarre, deep-seated sensory changes.

Since the hypothalamus weighs approximately four grams and is about 2.5 cm. in length, yet contains many different centers, pathologic lesions will be predominantly manifested by syndromes rather than isolated symptoms.

WATER METABOLISM AS AFFECTED BY HYPOTHALAMIC PATHOLOGY

Alterations in water metabolism without water deficit

Some of the critical points in the pathologic physiology of diabetes insipidus have been very precisely stated by Groethuysen and others (19). They reemphasize the lesions which are essential for the production of diabetes insipidus. An interruption of 50 per cent of the fibers of the supraoptico-hypophyseal tract caused diabetes insipidus in the cat. Lesions through the infundibulum, high enough to damage the median eminence had the same effect. Degenerative changes in the nucleus supraopticus as well as in the neuro-hypophysis with disappearance of pituicytes followed. These findings were interpreted by Fisher, Ingram and Ransom (12, 13) in the following way. "1) The hypothalamo-hypophyseal system constitutes an anatomic and functional unit. Nervous impulses arising from the supraoptic and paraventricular portions of this system regulate secretion of the antidiuretic principle by the neuro-hypophysis. 2) Diabetes insipidus is the result of deficient production of the antidiuretic principle within the neuro-hypophysis. 3) Polyuria in diabetes insipidus is primary and polydipsia secondary. 4) Thyroidectomy ameliorates but does not abolish diabetes insipidus. 5) Normally the anterior lobe of the pituitary influences diuresis, most likely indirectly by its controlling action over general metabolism."

While these five postulates have been generally accepted for the last fifteen years, the validity of the first three has more recently been challenged. Scharrer's conception of production of ADH (antidiuretic hormone) in the hypothalamus itself has at long last been accepted. He postulated (44) that ADH is secreted by the nuclei supraopticus and paraventricularis. The hormone droplets are transported along neural axons through the stalk into the posterior pituitary gland, where they are stored at the axon endings of the supraoptico-hypophyseal tract. From here ADH is released into the blood stream by nervous impulses arising in the nuclei just mentioned. Following its release, ADH acts upon the distal tubules of the kidneys to promote the reabsorption of water.

Three factors appear to act as trigger mechanisms in the release of ADH. First, the osmolar pressure of extracellular fluid; second, the volumetric changes in extracellular fluid, and third, the central nervous system response to direct stimulation. Verney has shown that an increase of two per cent in the osomotic pressure of extracellular fluid is sufficient to increase the rate of release of ADH (48, 49). Changes in blood volume

seem to have a similar effect but to a minor degree (46). Electrolyte changes also influence the release of this hormone. Emotional stress, pain and noise may induce release of antidiuretics by direct action upon the central nervous system.

As to the third point, that polydipsia is secondary to polyuria, this observation has recently been challenged by various observers. Greer, for instance, has found that electric stimulation of the hypothalamus in the region of the dorsomedial nuclei results in "violent drinking" in the rat (17). The same phenomenon has been demonstrated in dogs by electric stimulation of the middle part of the hypothalamus. Destruction of the same area produced transient loss of thirst (1).

An essential water deficit was found in the majority of cases of diabetes insipidus which we will discuss. The electrolyte balance, particularly for salt, was maintained, even though a huge amount of water was required to accomplish this. Therefore, hypernatremia and other marked electrolyte disturbances do not occur in these patients.

From the point of view of "drinking centers" in the hypothalamus it may be relevant to note that, of the 60 patients studied, 21 were reported to have had diabetes insipidus. However, if strict criteria for this condition were applied a small number of these patients did not seem to have diabetes insipidus but only an extreme polydipsia. In other words, they were able to concentrate their urine under certain conditions. These patients may have had lesions in the "drinking centers."

Fifteen of the 21 patients with diabetes insipidus cases had neuro-opthalmologic pathology. A combination of these two features should orient our diagnostic considerations to an anterior hypothalamic lesion. Other manifestations most frequently associated with diabetes insipidus were hypogonadism and obesity. These occurred in ten and nine cases, respectively. The presence of such conditions tended to localize the lesion in the anterior medial part of the hypothalamus, as will be discussed later. Precocious puberty, a syndrome resulting from posterior lesions of the diencephalon was seven times associated with diabetes insipidus. However, all of these precocious puberty cases had large lesions, affecting the whole floor of the third ventricle. Diabetes insipidus usually occurred later on in the sequence of events, apparently when the tumor had reached the anterior portion of the hypothalamus.

In eight out of the 21 diabetes insipidus patients, the pituitary gland was normal on microscopic examination.

The precipitating cause of diabetes insipidus in these 21 cases was neoplasm involving the third ventricle, *i.e.*, eight craniopharyngiomas and eight other brain tumors. Old inflammatory lesions of the periventricular structures were encountered in the five remaining cases. Of the remaining causes of diabetes insipidus none was encountered in this study of 60 cases. An excellent survey of the whole subject of diabetes insipidus can be found in Tice's *Practice of Medicine* (39).

Alterations of water metabolism with water deficit

Recently, Gordon and Cooper reported a group of approximately 30 cases including two of their own with cerebral lesions and severe hypernatremia and/or hyperchloremia in the absence of frank renal lesions (8, 15). In twenty-one instances there was definite involvement of the hypothalamus. Most of the other cases represented lesions in the frontal lobes. Values of 170 mEq./L of serum sodium and 130 mEq./L of serum chlorides were found in some patients. After carefully sifting the evidence, these authors concluded that these patients had a true "neurogenic" type of hypernatremia. They referred to the experiments of Lewy and Gassman, who obtained hyperchloremia in cats following electrical stimulation of the paroptic nucleus in the hypothalamus (31). Stevenson was able to produce chronic hypodypsia and hyper-

natremia in rats with lesions of the ventromedial nuclei, who were taking water *per os* only (47). Cooper (8) studied a patient with hypernatremia and hyperchloremia, in whom excessive hydration was carried to the point of water intoxication; however, the hypertonicity of the blood was not changed through this procedure. Gordon (15) feels that faulty neurogenic osmolar regulation of the blood may first lead to water deficit. According to Gordon, the events following this, which lead to the severe hypernatremia and other manifestations are an expression of the physiologic response to the water deficit. He refers to Welt's review of this subject (51). In the opinion of this author, the earliest and most important response to water deficit is a concentration of sodium in the extracellular fluid. This is followed by a transfer of water from the cells into the extracellular compartments. The cellular dehydration is supposed to decrease the rate of sweating and insensible perspiration. At the same time the sensation of thirst is created. A contracted plasma volume is the next consequence of the depletion of all body fluids. This contraction of plasma volume stimulates reabsorption of salt by the tubules. This has been called the "dehydration reaction" (Peters, 40). Another contributing factor to salt retention is the increased rate of secretion of aldosterone in response to water deficit (3).

Recently, L. G. Farrell (11) has furnished considerable evidence that cerebral centers in the neighborhood of the epiphysis may have an effect on the preservation of a stable blood volume even at the expense of osmolar pressure homeostasis. Activity of these centers induced by volume contraction would lead to increased aldosterone secretion, and thus hypernatremia, in patients with a "water deficit" as described here.

Regardless of the answer to these theoretical questions, it may be useful to carry out water and electrolyte balance studies in all patients with severe cerebral injury.

SEXUAL DEVELOPMENT AND MAINTENANCE OF FUNCTION AS INFLUENCED BY THE HYPOTHALAMUS

Sexual development and maintenance of sex function seem to be quite closely associated with the activity of hypothalamic centers. Sections of the infundibular stem at different levels have given widely variant, at times apparently contradictory results. This was partly due to the fact that many investigators did not take into consideration the pars tuberalis of the hypophysis, a secretory section of this gland, situated high up on the infundibular stem, which is in close contact with the anterior, inferior sections of the hypothalamus. Secondly, unawareness of the importance of regeneration or lack of regeneration of the portal circulation system after stalk severance may have further beclouded the true situation. Finally, it has been demonstrated that not direct nervous control but neuro-humoral mechanisms act *via* diencephalic centers to effect the release of gonadotrophic hormones from the hypophysis (26); the portal circulation system, affords the channels through which the humoral agents reach the anterior pituitary gland. In 1946 Markee was able to demonstrate ovulation following electric stimulation of the hypothalamus (35). Stimulation of the adenohypophysis did not have this effect. After various other preliminary steps of investigation the following sequence of events has been reported by Sawyer (43). The act of mating in rabbits leads to nervous activity in hypothalamic centers and the release of acetylcholine during the first 15 seconds after mating. One minute later noradrenaline is released, probably in the median eminence and is transported *via* the portal circulation into the adenohypophysis where it releases gonadotrophic hormone resulting in ovulation. Estrogen and progesterone work synergistically in stimulating release of luteinizing hormone *via* hypothalamic centers (47). Noradrenaline seems to be the actual releasing substance, as suggested by Sawyer. Most

nuclei responsible for stimulation of sex function are concentrated in the tuber cinereum. Lesions in the paraventricular and ventromedial nuclei lead to depression of gonadal function. Experimental evidence regarding hypothalamic mediation of sex functions as well as of other endocrine activities has been recently surveyed by Cleghorn (6).

In collecting cases with hypothalamic pathology from the literature only those were included which have been adequately autopsied. A further element of selection did enter into the results because of the two series of cases of sexual abnormalities. However, many more cases than the ones reported in this group of 60 were studied, and the definite impression was that gonadal dysfunction is a very frequent manifestation of hypothalamic pathology. As a matter of fact gonadal dysfunction is an early sign in patients with diencephalic pathology. In our group of 60 patients, 43 had such abnormalities. In 33 of 35 of them the pituitary gland was grossly normal, a finding confirmed microscopically in all of the cases so studied.

PRECOCIOUS PUBERTY

Precocious puberty occurred in 24 cases, 19 males and five females. In 13 patients, large portions of the hypothalamus were involved. In 11 the lesions were small. In five instances, minute congenital malformations were attached to the corpora mamillaria or the tuber cinereum. They contained tissue elements, normally present in the latter structure.

There was no overt damage to the hypothalamic centers in any of these five cases.

The pituitaries of all 24 cases of precocious puberty were normal, a fact confirmed by histological examination in 20 cases. Premature release of gonadotrophic hormones *via* lesions in inhibitory centers, such as the corpora mamillaria have been postulated by Weinberger to explain this form of precocious puberty (50).

Eye signs and diabetes insipidus occurred in seven (29 per cent) of these 24 patients with pubertas praecox. In contrast, 75 per cent of the total number of patients with diabetes insipidus exhibited eye signs. The infrequency of both, ophthalmologic conditions and of diabetes insipidus in the patients with precocious puberty is confirmatory of the posterior location of hypothalamic lesions in this abnormality of sexual development. In other cases of diabetes insipidus obesity was associated five times as frequently. Somnolence did not occur in any of the patients afflicted with precocious puberty.

HYPOGONADISM

There were 19 cases of hypogonadism among the 60 patients, 12 males and seven females. In contrast to precocious puberty, the association with diabetes insipidus and obesity was much more prevalent in this group, being observed in nine and in eight cases respectively. The predominant site of lesions was in the anterior hypothalamus. Craniopharyngioma was the most frequently observed neoplastic lesion in all 60 of the cases reviewed, being present in 14 patients. This new growth was responsible for the development of hypogonadism in nine patients. The origin of these tumors from remnants of the hypophyseal duct has been mentioned above. They attack the frontal part of the hypothalamus first. While the timing of release of gonadotrophic hormones towards adolescence seems to be a function of posterior hypothalamic centers, and possibly the corpora mamillaria or the posterior infundibulum, the stimulation of sexual activity seems to be influenced by more anteriorly situated centers, such as the tuber cinereum and the median eminence. Therefore, the signs which were found to be relatively infrequent in precocious puberty were found much more frequently in hypogonadism. Thus, eye signs were present in 52 per cent of the latter patients, diabetes insipidus in 47 per cent and obesity in 42 per cent. Often the sequence of the appearance of signs in the hypogonadal patients with craniopha-

ryngioma was: eye signs, diabetes insipidus, obesity and hypogonadism. This well described the path of progression of this tumor. Of course, if and when internal hydrocephalous supervenes, the whole picture may change. Moreover, internal hydrocephalus caused by distant tumors, especially posterior fossa neoplasms, may lead to hypothalamic symptoms as explained above. In four of the 60 cases with hypothalamic neoplasm a tentative diagnosis of posterior fossa tumor was made. In three of these a suboccipital craniotomy was performed, with negative findings.

ASSOCIATION OF HYPOGONADISM WITH DYSTHERMIA

The association of hypogonadism with dysthermia occurred in nearly half (28 cases) of the 60 patients studied. This may not be surprising if it is realized that temperature-regulating centers are scattered through the hypothalamus but mainly concentrated in the anterior diencephalon. There is a heat-dissipating center in the so called preoptic region. This center reacts to rising blood temperatures by initiating stimuli which result in panting, increased peripheral blood flow and perspiration. Pathways arising in the preoptic region and going down in to the brain stem are used to effect these reactions (41). Centers for heat production and heat maintenance are widely scattered through the hypothalamus, but are partly also concentrated below the supraoptic region. These centers or cells preserve or elevate heat by stimulating such processes as vasoconstriction, shivering and increase of metabolism. The latter is probably accomplished through neurohumoral mechanisms in the hypothalamus affecting an increased rate of release of thyroid stimulating hormone from the adenohypophysis. Lesions in the "lateral areas" of the hypothalamus, situated more caudally, may depress both of the former thermoregulatory centers and thus cause a state of poikilothermia (27). Dysthermia, including poikilothermia, occurred in 13 of the 60 patients, while the association of hypogonadism and dysthermia was observed in more than twice as many cases, as mentioned above. This might indicate a preference for the occurrence of this latter combination.

OBESITY AND ITS ASSOCIATION WITH OTHER MANIFESTATIONS OF HYPOTHALAMIC DYSFUNCTION

Various observers have attempted to link hypothalamic obesity to simultaneous diencephalic thermodysregulation. The diffuse distribution of thermoregulatory centers and the role of metabolism in the production of dysthermia indicate not one but a combination of etiologic factors. Furthermore, the combination of hypogonadism and obesity has been emphasized by many investigators, because of the occurrence of both of these conditions in the majority of lesions affecting the ventromedial nuclei, and because of the appearance in the dystrophia adiposo-genitalis or Froehlich's syndrome (14). However, this concept seems to need modification. Of the 19 hypogonadal patients with hypothalamic pathology, nine were obese, four of normal build and six emaciated. It would appear that the association of hypogonadism and obesity in patients with hypothalamic lesions is not obligatory. In 1901 Froehlich reported a case of adenohypophyseal tumor in a 14 year old boy who revealed hypogenitalism and the pectoral girdle type of obesity with feminine features. Froehlich attributed this syndrome to pituitary dysfunction. Later on, numerous reports appeared in the literature showing that the same syndrome occurs with lesions strictly confined to the hypothalamus. When the case of Froehlich was carefully reviewed, it was found that the pituitary tumor had exerted pressure on the hypothalamus. Most observers now believe that involvement of the hypothalamus is essential for the production of dystrophic adiposogenitalis. A few workers, Cushing for instance, have maintained that, in some cases, lesions

strictly confined to the pituitary gland may cause this syndrome (9). One wonders, however, if a tumor inside the sella may not interfere with hypothalamic function by producing tension on the stalk and thus variations in the portal circulation. In this case survey of 60 patients a grossly normal hypophysis was revealed by autopsy in 14 of the 16 hypogonadal cases. The normalcy was confirmed histologically in ten cases.

Aside from these organic hypothalamic lesions, there is a large group of stout, slightly hypogonadal children, who unfortunately are termed instances of "Froehlich's syndrome." Actually, these adolescents represent only a transient functional insufficiency of the diencephalic mechanisms of adaptation. In other words the extremely complex task of integration of advancing growth, maturation of gonads and psychologic adjustment of the changing individual to social environment is not always smoothly handled by the diencephalon. Almost all of these cases come again into equilibrium, some of these in spite of interfering hormonal treatment.

However, if diabetes insipidus, dysthermia, psychiatric disturbances or somnolence complicate this syndrome a thorough search for a brain lesion should be made. Somnolence was associated with the 19 hypogonadal cases in seven instances, and psychiatric disturbances in five cases. Psychotic behavior thus was encountered in one-quarter of the hypogonadal patients. It occurred in approximately the same proportion (28.5 per cent) of all 60 cases. The importance of the hypothalamus regarding mental states and behavior has been greatly and justly emphasized in the current psychiatric literature.

Obesity was a sign of hypothalamic pathology in fifteen of the 60 cases studied. Emaciation occurred in eleven cases, bulimia in five and anorexia in four patients. The question of hypothalamic obesity due to hyperphagia *per se* or due to associated metabolic alterations is not yet settled. Two key structures in the diencephalon have to be considered in this problem; the ventromedial nuclei and the lateral hypothalamic areas or so-called feeding centers. Excessive obesity has been produced in rats by bilateral lesions in the ventromedial nuclei, as reported by Hetherinton and Ranson (25). Heinbeckers' lesions in the paraventricular nuclei, accompanied by obesity apparently affected descending fibers of the ventromedial nuclei according to Mayer (24, 36). Lesions of the latter nuclei produce obesity in association with a savage behavior of the animal, depression of the gonads and frequently changes in metabolism, especially blood sugar level changes. The feeding centers or lateral areas of the hypothalamus are situated laterally to the ventromedial nuclei. Stimulation of these centers results in hyperphagia, unassociated with psychic, metabolic or gonadal changes (10). Unfortunately not enough reports of the metabolic function tests in the obese patients were available to draw any inferences.

A triad of hypogonadism, obesity and diabetes insipidus occurred in four cases; hypogonadism, dysthermia and diabetes insipidus in five; hypogonadism, obesity and dysthermia in six patients of this group of 60 cases. These figures do not seem to indicate any prevalence of the occurrence of the three triads. It is well understood that obesity is not only a question of hypothalamic dysfunction, but also of genetic and environmental factors. Jean Mayer (36) and Gelvin and McGavack (38) have written comprehensive reviews on this complex topic.

THE RELEASE OF ACTH AND ADRENOCORTICAL FUNCTION AS INFLUENCED BY HYPOTHALAMIC PATHOLOGY

While there is definite evidence of hypothalamic adjustment in the release of ACTH and its consequent action upon adrenocortical functions, it is equally clear that the degree of adrenocortical atrophy obtained by hypophysectomy has never been matched by any manipulations affecting the hypothalamus. Lesions in the median eminence

and adjacent hypothalamic centers were found to be associated with a decrease in the eosinopenia and in the decline of steroids in the adrenal vein blood after stress (30, 37). Long and Fortier demonstrated a dual type of control of ACTH release (33). The release of ACTH following painful stimuli or laparotomy is accomplished by hypothalamic control. ACTH release following epinephrine, cold exposure and other "somatic" stress is not controlled by the diencephalon. Diencephalic lesions which block this type of control have to be in the plane of the paraventricular nuclei and in the area just behind these nuclei. This is in the area of the anterior and medial part of the median eminence, in the plane of the ventromedial nuclei. Long (33) concludes, "it is now commonly agreed that the median eminence is the essential factor for ACTH release." There is also general consensus of opinion that stimulation of the median eminence and posterior hypothalamic centers results in release of ACTH as judged by a drop of circulating eosinophiles and lymphocytes. This effect is not dependent on long descending pathways. It is accomplished by the release of noradrenalin and acetylcholine from nerve fiber endings in the median eminence, and the transport of these neurohumoral agents *via* the portal circulation into the adenohypophysis. ACTH is then finally released from this gland.

Two other humoral agents may be implicated in the diencephalic control of ACTH release. The first is vasopressin. There is suggestive evidence that this "neurohormone" may act as an "activating" substance in regard to release of the corticotrophic hormone. McCann and Brobeck believe that release of vasopressin into portal vessels causes ACTH release (37). The second agent for ACTH release might be secreted in the hypothalamus itself. Hellerstein has shown that daily injections of hypothalamic beef extract into rats resulted in greater lymphopenic responses than medulla oblongata injections into litter mates (22). He suggests that hypothalamic centers secrete a specific neurohormone for the release of ACTH.

Recently it has been possible to culture adenohypophyseal tissues *in vitro* with very good differentiation of cell elements. Substances, suspected to influence ACTH release, were added. The combination of epinephrine, norepinephrine and hypothalamic tissues caused a threefold increase in the rate of ACTH release from the pituitary tissues. Any one of the three substances by itself had no such effect. The largest increase of ACTH release was obtained by adding posterior pituitary extract and norepinephrine in combination (42).

To return to the group of 60 surveyed patients it is surprising that among 14 patients whose adrenals were carefully examined only three had slight indications of adrenal pathology. Of course, in selecting these patients, care was taken not to include patients with intensive involvement of the hypophysis. Considering this, one might say then that the effect of hypothalamic control of the adrenals must be one of fine adjustment only. It might be of interest to discuss in detail the three cases in whom some degree of pathology of the adrenal glands was found.

Case No. 1. The first case was that of a 29 year old female (7). A craniopharyngioma had destroyed all the nuclei of the hypothalamus. The adenohypophysis was intact grossly as well as on microscopic examination. However, the posterior lobe showed marked atrophy of cellular elements. All nerve fibers in the stalk were degenerated. The thyroid showed lymphocytic infiltration, epithelial metaplasia and low cuboidal epithelium of the follicles. The adrenal glands were small with a decrease in the number of cells in each of the three zones. There was strong evidence of depression of the genital organs. In the autopsy report, it was concluded that there was marked impairment of the trophic factors of gonads, thyroid and adrenal cortex via the destruction of all hypothalamic nuclei. In addition

to the patient's hypogonadal features, she had diabetes insipidus, hypothyroidism, requiring intake of thyroid gland, a diabetes mellitus-like condition and marked psychiatric disturbances. She also suffered from somnolence, dysthermia, vaso-motor instability and obesity. She had no real clinical manifestations of hypoadrenocorticism. Perhaps her diabetes mellitus might have been more severe if adrenocortical function had been indubitably normal. On the other hand, her lowered thyroid function may have been responsible primarily for whatever mild pathology she had in her adrenal glands. The atrophy of posterior lobe tissue and nerve fibers in the stalk was secondary to the destruction of the supraoptic and paraventricular nuclei. The role of vasopressin and antidiuretic hormone as possible activating substances for the release of ACTH has been mentioned above. One might speculate that the absence of these substances was the reason for the cortical changes. Aside from the highly theoretical aspects of these mechanisms this would still be rather doubtful, since among 21 cases of diabetes insipidus only two patients had autopsy findings suggesting very mild depression of cortical function. Of course, the diabetes insipidus in this patient is fully explained on the basis of total destruction of the centers responsible for release of antidiuretic hormone.

Case No. 2. The second patient was a 23 year old man (5). A pinealoma had involved the floor of the third ventricle and its anterior wall. The mamillary bodies were flattened by the tumor and the aqueduct of Sylvius blocked. There was internal hydrocephalus of the third and lateral ventricles. Many hypothalamic cells showed vacuolar degeneration. The pituitary gland was somewhat depressed but normal on microscopic examination. The testes showed marked hyaline degeneration of the tubules and masses of leydig cells. The combined weight of the adrenal glands was "only 9.5 gm.—average 17.0 gm.—" but they were microscopically normal. This man had clinical manifestations of hypogonadism, such as absence of facial hair and female escutcheon. The size of his testes gradually changed from walnut to marble size after the age of 17 years. Partial sexual function, at least penile erection, seemed to have been preserved since this patient was known to have masturbated frequently. This clinical picture of impaired sexual function was based predominantly on failure of the tubular apparatus of the testes, as just mentioned. In addition, he displayed somnolence, emaciation, psychic disturbances, bulimia and urinary incontinence. It is stated in the history that this patient had a voracious appetite, and yet he lost weight—37 pounds within three years—while overeating. There were no debilitating features during this phase. The patient did not present any clinical signs of depression of the adrenal glands.

Case No. 3. The third case is that of a 15 year old boy (2). He had a syndrome of hypogonadism, diabetes insipidus, dysthermia, initially emaciation, later followed by obesity and psychiatric disturbances. This patient also had somewhat low metabolic rates. A pinealoma had invaded the third ventricle and the posterior lobe of the pituitary gland. The adenohypophysis was normal in all regards. The adrenal cortex of both glands was described as very thin. Both glands were small. The sequence of emaciation and obesity in this boy is interesting. Pinealomas, because of their origin, would impinge on the hypothalamus from the back first. However in many of these tumors metastatic implantations on the walls or floor of the third ventricle were seen. This, of course, may change the picture of invasion from the back to one of anterior as well as posterior involvement. In some cases the metastatic implantation, if it occurs more anteriorly, may represent the initial hypothalamic lesion, while the original tumor has not yet reached the posterior hypothalamus. Anorexia could have followed the destruction of the lateral feeding centers,

while obesity would be a consequence of impairment of the ventromedial nuclei. It is very hard to see, however, why the lateral hypothalamic areas should be destroyed first by a pinealoma or metastatic implants of it. There were no clinical signs of adrenocortical dysfunction in this boy.

BLOOD PROTEIN DISTURBANCES

White and Dougherty have indicated that the supply of globulin to the blood is under the control of the anterior pituitary gland (52, 53). ACTH secreted by this gland and the subsequent secretion of 11-oxygenated corticoids is supposed to control this supply. As mentioned above, hypothalamic control of most of the secretions of the adenohypophysis is strongly suggested by the accumulated evidence in this field. It seems appropriate therefore to mention the following cases reported by Lomax (32). This author described seven cases with invasion of the third ventricle and abnormal serum protein levels. The principal abnormality was a decrease of the A/G ratio, caused by an increase of globulin. All of these patients were ambulant while their blood chemistry was examined. One patient who had special studies, showed a normal nitrogen balance. Of 44 other patients with brain tumors or other space occupying lesions, not invading the third ventricle, none had abnormal protein levels in the blood. There is no evidence of disturbed protein levels in patients with panhypopituitarism. None of the group of 60 patients examined for protein levels, showed any abnormality.

THE RELEASE OF THYROID STIMULATING HORMONE AND THYROID FUNCTION

Cleghorn in his review "The hypothalamic endocrine system" mentions the fact that environmental as well as emotional factors influence the rate of thyroid secretion (6). This may indicate some hypothalamic control of TSH (thyroid stimulating hormone) release. In 1952 Greer was able to show that certain hypothalamic lesions interfered with pituitary stimulation of growth of thyroid cells concerned with the secretion of thyroxine, while the stimulation of iodine metabolism was still intact (16). He concluded that stimulation of growth of the thyroid is dependent on the hypothalamus, while iodine metabolism is dependent only upon stimulation by the adenohypophysis. In 1953 (45) the same author and Scow demonstrated that intact mice have a higher I-131 uptake than hypophysectomized mice with functioning intraocular pituitary implants, *i.e.*, animals in whom the contiguity with the hypothalamus has been interrupted completely, while the adenohypophysis still functions. The compensatory thyroid growth response to propylthiouracil was prevented in the animals with ocular implants. There was marked increase of thyroid serum I-131 ratio in these operated animals. In the intact animals there was little increase of this ratio after propylthiouracil intake but a threefold increase in thyroid weight. These data confirmed the interpretation of Greer's first experiments. He had found that the most effective lesions for blocking thyroid growth were dorsal to the ventromedian nuclei in the region of the median eminence, 0.5 mm. lateral to the midline. It was mentioned above that lesions in the median eminence interfere with ACTH release. These lesions, however, are quite close to the midline in the anterior region of the median eminence. In 1955 Greer (18) demonstrated that lesions 0.5 mm. lateral to the midline did not interfere with the mechanism of ACTH release. However, they did interfere with the known goitrogenic response to amphenone. Amphenone produces both thyroid as well as adrenal cortex hypertrophy, but the latter hypertrophy was not prevented by these more lateral lesions. In other words, this was strongly suggestive evidence for separate hypothalamic centers controlling ACTH and TSH release. Radioactively labeled thyroxin accumulates in the neurohypophysis, tuber cinereum, and median eminence (28). Levine and Goldstein

concluded from these experiments that thyroxin deficiency acts in hypothalamic centers to control TSH release. However, the direct influence of thyroxin blood levels on the adenohypophysis also regulates TSH release as shown by Greer (45). Both mechanisms therefore seem to be utilized by the organism.

The basal metabolic rates were low or borderline low in nine of the ten cases which were reported. The pituitary gland was normal in six of these nine patients. There was no report of definite myxedema in any instance. One patient had basal metabolic rates as low as −43 per cent. Basal metabolic rates ranged from −11 per cent to −43 per cent. These findings can be well correlated with the above mentioned experimental evidence. Apparently iodine metabolism is not as much affected by hypothalamic lesions as the capacity for growth response of the thyroid epithelium of the follicles. Another of these patients also had low basal metabolic rates but no remarkable findings in regard to the thyroid at autopsy. Some patients had rather low basal metabolic rates and yet clinically no correlating signs.

If one compares the effect of hypothalamic pathology on adenohypophyseal release of the trophic hormones, the gonadotrophic principle seems to be most strongly affected, thyrotrophic principle weakly and adrenotrophic principle hardly at all.

SUMMARY

The clinical case material of 100 patients, with hypothalamic pathology selected from the literature, has been surveyed. In the great majority of these cases autopsy or at lease surgical evidence of hypothalamic invasion by neoplasm or other pathology was available. The effect of such hypothalamic pathology in water metabolism, electrolyte balance and release of trophic hormones from the adenohypophysis has been discussed. Experimental evidence and clinical findings in these cases have been compared in regard to each of these individual phases of hypothalamic control. As far as the effect of disturbed hypothalamic functions on the target organs is concerned the gonads appeared to be most strongly impaired, the thyroid slightly and the adrenal cortices least. Disturbances, of water metabolism, mainly diabetes insipidus, occurred in direct proportion to the destruction of the commonly accepted control centers. However, in a group of 30 patients with severe traumatic brain lesions and marked hypertonicity of the blood the question of impairment of other centers regulating electrolyte balance, as suggested in animal experimentation was raised. Another group of seven patients with hypothalamic pathology and disturbed blood protein levels has also been discussed.

REFERENCES

1. Anderson, B. and McCann, S. M. Polydypsia evoked by hypothalamic stimulation in the goat. (abstr.) Fed. Proc., **15**: 4, 1956.
2. Bailey, P. and Fulton, J. Tumors in the region of the third ventricle, their diagnosis and relation to pathologic sleep. J. Nerv. & Ment. Dis., **69**: 1, 1929.
3. Barter, F. C. The role of aldosterone in homeostasis and certain disease states. Metabolism, **5**: 369, 1956.
4. Bauer, H. G. Endocrine and other clinical manifestations of hypothalamic disease. J. Clin. Endocrinol., **14**: 13–31, 1954.
5. Cleghorn, R. A. Hypogonadism associated with invasion of the midbrain and hypothalamus. Quart. J. Med., **7**: 183–209, 1938.
6. Cleghorn, R. A. The hypothalamus-endocrine system. Psychosom. Med., **17**: 367–376, 1955.
7. Collins, V. P. Effects of destruction of hypothalamus by tumor. Arch. Neurol. & Psychiat. **46**: 774–788, 1938.
8. Cooper, I. S. and Crevier, P. H. Neurogenic hypernatremia and hyperchloremia. J. Clin. Endocrinol., **12**: 821–830, 1952.
9. Cushing, H. *Papers relating to the pituitary body, hypothalamus and parasympathetic nervous system.* C. Thomas, Springfield, Ill., 1932.
10. Delgado, J. M. R. and Anand, B. K. Increase in food intake induced by electric stimulation of lateral hypothalamus. Am. J. Physiol., **172**: 162–168, 1953.
11. Farrell, G. L. The physiological factors which influence the secretion of aldosterone. In press.
12. Fisher, C. Diabetes insipidus and the neurohormonal control of water balance. (abstr.) Proc. Inst. Med. Chicago, **13**: 117, 1940.

13. Fisher, C., Ingram, W. R. and Ranson, S. W. *Diabetes insipidus and the neuro-hormonal control of water balance; a contribution to the structure and functions of the hypothalamo-hypophyseal system.* Edwards Bro., Inc., Ann Arbor, Mich., 1938.
14. Froelich, A. A case of tumor of the hypophysis without acromegaly. A. Res. Nerv. & Ment. Dis., Proc., **20:** 16–28, 1940.
15. Gordon, G. L. and Goldner, F. Hypernatremia, azotemia and acidosis after cerebral injury. Am. J. Med. **23:** 543–553, 1957.
16. Greer, M. A. Role of hypothalamus in control of thyroid function. J. Clin. Endocrinol., **12:** 1259–1268, 1952.
17. Greer, M. A. Suggestion of a primary "drinking" center in hypothalamus of the rat. Proc. Soc. Exper. Biol. & Med., **89:** 59–62, 1955.
18. Greer, M. A. and Erwin, H. Evidence of separate hypothalamic centers, controlling corticotrophin and thyrotrophin secretion by the pituitary. J. Clin. Endocrinol., **15:** 839, 1955.
19. Groethuysen, U. C., Clark, E. C., Randall, R. V. and Dodge, H. W. The neurogenic basis of diabetes insipidus, a review. Proc. Staff Meet. Mayo Clin. **32:** 90–98, 1957.
20. Harris, G. W. Recent advances concerning the relationship between the hypothalamus and pituitary gland. Acta physiol. et pharmacol. neerl., **3:** 289–98, 1954.
21. Harris, G. W. and Fortier, C. *Fourth annual report on stress.* Acta Inc., Montreal, Canada, 1955.
22. Hellerstein, S., Holtkamp, D. E., Hickey, M. E., Hill, R. N. and Buchanan, A. R. Effect of hypothalamic extract on leucocytes of infant rats. Am. J. Physiol., **171:** 106–113, 1952.
23. Heinbecker, P. The pathogenesis of Cushings syndrome. Medicine, **23:** 225, 1944.
24. Heinbecker, P., White, H. C. and Rolf, D. Experimental obesity in dog. Am. J. Phvsiol., **141:** 549–565, 1944.
25. Hetherington, A. W. and Ranson, S. W. Relation of voracious appetite in hypothalamic lesions to adiposity in rat. Am. J. Physiol., **136:** 609–617, 1942.
26. Hinsey, J. C. and Markee, J. E. Studies of prolan induced ovulation in midbrain and in midbrain hypophysectomized rabbits. Am. J. Physiol., **106:** 48–54, 1933.
27. Ingram, W. R. The hypothalamus. Clin. symposia, Ciba, **8:** 117–56, 1956.
28. Jensen, J. M. and Clark, D. E. Localization of radioactive 1-thyroxin in neurohypophysis. J. Lab. & Clin. Med., **38:** 663, 1951.
29. Kestenbaum, A. *Clinical methods of neuro-ophthalmologic examination,* p. 65. Grune & Stratton, New York, 1947.
30. Lacquer, G. L., McCann, S. M., Schreiner, L. H., Rosenberg, E., Rioch, D. M. and Anderson, E. Alterations of adrenal cortical and ovarian activity following hypothalamic lesions, based on eosinophile response, hormone assay and histological examination. Endocrinology, **57:** 44–54, 1955.
31. Lewy, F. H. and Gassman, F. K. Experiments on the hypothalamic nuclei in the regulation of chloride and sugar metabolism. Am. J. Physiol., **112:** 504–510, 1935.
32. Lomax, P. Lesions of the hypothalamic region and serum protein levels. Lancet, **272:** 904–907, 1957.
33. Long, C. N. H. Pituitary adrenal relationships. Ann. Rev. Physiol., **18:** 409–432, 1956.
34. Markee, J. E., Everett, J. W. and Sawyer, C. H. The relationship of the nervous system to the release of gonadotrophic hormone and the regulation of sex cycle. Recent Progr. Hormone Res., **7:** 139, 1952.
35. Markee, J. E., Sawyer, G. H. and Hollinshead, W. H. Activation of anterior hypophysis by electric stimulation in rabbits. Endocrinology, **38:** 345–357, 1946.
36. Mayer, J. Genetic, traumatic and environmental factors in the etiology of obesity. Physiol. Rev., **33:** 472–508, 1953.
37. McCann, S. M. and Brobeck, J. R. Evidence for a role of the supraopticohypophyseal system in regulation of adreno-corticotrophin secretion. Proc. Soc. Exper. Biol. & Med., **87:** 318–324, 1954.
38. McGavack, T. H. *Obesity.* Hoeber-Harper, New York, 1957.
39. McGavack, T. H. Diabetes insipidus. In *Tice's Pract. of Med.,* In press.
40. Peters, J. P. Sodium, water and edema. J. Mt. Sinai Hosp. New York, **17:** 159–175, 1950.
41. Ranson, S. W. Regulation of body temperature. A. Rec. Nerv. & Ment. Dis., Proc., **20:** 342–399, 1940.
42. Saffran, M. and Schally, A. V. The release of corticotrophin by anterior pituitary tissue in vitro. Canad. J. Biochem. & Physiol., **33:** 408–415, 1955.
43. Sawyer, C. H., Markee, J. E. and Everett, J. W. Blockade of neurogenic stimulation of the rabbit adenohypophysis by banthine. Am. J. Physiol., **166:** 223–228, 1951.
44. Scharrer, E. and Scharrer, B. Hormones produced by neuro-secretory cells. Recent Progr. Hormone Res. **10:** 183, 1954.
45. Scow, R. O. and Greer, M. A. Observation on the control of thyrotropin secretion of intraocular pituitary implants in hypophysectomized rats. J. Clin. Endocrinol., **13:** 855, 1953.
46. Smith, H. W. Renal excretion of sodium and water. Fed. Proc., **11:** 701–705, 1952.
47. Stevenson, J. A. F., Welt, L. G. and Orloff, J. Abnormalities in water and electrolyte metabolism in rats with hypothalamic lesions. Am. J. Physiol., **161:** 35–39, 1950.
48. Verney, E. B. Absorption and excretion of water; the antidiuretic hormone. Lancet, **2:** 739–744; 781–783, 1946.
49. Verney, E. B. Croonian lecture; the antidiuretic hormone and the factors which determine its release. Proc. Roy. Soc. London. Ser. B, **135:** 25–106, 1947.
50. Weinberger, L. M. and Grant, F. C. Precocious puberty and tumor of hypothalamus, report

of case in review of literature with pathophysiologic explanation of precocious sexual syndrome. Arch. Int. Med. **67**: 762–792, 1941.

51. Welt, L. G., Seldon, D. W., Nelson, W. B. III, German, W. J. and Peters, J. P. Role of the central nervous system in metabolism of electrolytes and water. A. M. A. Arch. Int. Med. **90**: 335–378, 1952.
52. White, A. and Dougherty, T. F. Influence of pituitary adrenotrophic hormone on lymphoid tissue structure in relation to a serum protein. Proc. Soc. Exper. Biol. & Med. **56**: 26, 1944.
53. White, A. and Dougherty, T. F. Role of lymphocytes in normal and immune globulin production, and mode of release of globulin from lymphocytes. Ann. New York Acad. Sc., **46**: 859–882, 1946.
54. Wislocki, G. B. The vascular supply of the hypothalamus cerebri of the cat. Anat. Rec., **69**: 361–87, 1937.
55. Wislocki, G. B. Further observations on the blood supply of the hypothalamus cerebri of the rhesus monkey. Anat. Rec., **72**: 137–150, 1938.
56. Wislocki, G. B. The vascular supply of the hypothalamus cerebri of the rhesus monkey and of man. A. Res. Nerv. & Ment. Dis., Proc., **17**: 48–68, 1938.
57. Wislocki, G. B. and King, L. S. The permeability of the hypophysis and the hypothalamus to vital dyes with a study of the hypophyseal vascular supply. Am. J. Anat., **58**: 421–472, 1936.
58. Xuereb, G. P., Prichard, M. M. L. and Daniel, P. M. The arterial supply and venous drainage of the human hypophysis cerebri. Quart. J. Exper. Physiol., **39**: 199, 1954.
59. Xuereb, G. P., Pritchard, M. M. L. and Daniel, P. M. The hypophyseal portal system of vessels of man. Quart. J. Exper. Physiol., **39**: 219, 1954.

EMOTIONAL ACTIVATION OF THE ELECTROENCEPHALOGRAM IN PATIENTS WITH CONVULSIVE DISORDERS

JANICE R. STEVENS, M.D.[1]

In the more than 2,000 years that have passed since the earliest preserved written accounts of epilepsy appeared in the Hippocratean collection of medical manuscripts, much has been added to the clinical description of the convulsive syndrome. Appreciation of the variety and scope of clinical epileptic patterns reached its culmination in the writings of Hughlings Jackson, Gowers and Herpin the late 19th century (8, 12, 14). Bioelectric components of seizure activity have become known to us only in the past 30 years and remarkable impetus to the investigation of convulsive states has attended the use of electroencephalography. The pioneering studies of Penfield and Jasper, Gibbs and Gibbs and their associates (7, 15, 25) have demonstrated the relationship of certain clinical seizures to focal pathological electrical discharge in the brain, ushering in an era in which epilepsy is distinctly linked to physiological or structural brain damage, is subject to replication by appropriate electrical stimulation of the brain, and is abolished in many instances by surgical removal of faulty cerebral tissue.

Despite these significant advances in our knowledge of convulsive disorders, remarkably little new information concerning the immediate or precipitating causes of a particular epileptic attack has emerged. Given a cortical scar, or a spike discharge on the electroencephalogram, what other events determine that at a certain moment a frank epileptic attack will occur? The answer to this question is now little clearer than it was at the dawn of medical history.

That emotional agitation may precipitate the epileptic attack in those so predisposed has long been recognized, and is documented in poetry and prose as well as in medical literature since antiquity.

Hughlings Jackson stated that peripheral sensory stimuli and strong emotion may precipitate or even cause epileptic seizures, but emphasized that it is the *neural* accompaniment of the emotionally excited state, which discharging into an area of hyperirritable nerve tissue constitutes the physiological basis of the attack (14).

In recent times, the search for causative factors in epilepsy has ranged in two principal directions. Firstly, the elucidation of those factors responsible for pathologically increased central irritability and secondly, investigation of internal and external environmental stimuli necessary to or capable of surpassing a continuously fluctuating epileptogenic threshold.

It is with the latter "input" component, the "external irritations" of Hughlings Jackson, that we have been concerned in our laboratory. A number of factors have interested us in exploration of the effects of emotional stress on the electroencephalogram of individuals subject to epileptic seizures. Foremost has been the history frequently obtained from certain patients indicating the regular concurrence of epileptic seizures with unusual excitement, or perhaps with equal likelihood, the appearance of attacks in the minutes or hours following an acute emotional disturbance. Not a few patients report mounting tension and irritability which builds up progressively during the interval between seizures and reaches a maximum in the hours or minutes

[1] Division of Neurology, University of Oregon Medical School, Portland, Oregon. This investigation, supported by Public Health Service Grant No. B-1140, was presented in part at the American EEG Society, October, 1957. The author wishes to acknowledge with thanks the assistance of Miss Jacquetta Nelson and Dr. John Watkins of the U. S. Veteran's Hospital, Portland, Oregon.

immediately preceding a frank seizure. This tension is characteristically relieved by the occurrence of a seizure.

In addition to the possible effect of emotional stress on the occurrence of epileptiform activity in the electroencephalogram, it is of particular interest to determine whether specific regions of the cerebrum are unusually susceptible to such activation. Recent studies indicating that the temporal lobe and underlying rhinencephalic structures may be concerned with emotional appreciation and expression (6, 16, 17, 21, 24, 26) led us to question whether the electrical manifestations of convulsive disorder originating in this area might be particularly affected during emotional stimulation.

MATERIALS AND METHODS

The effect of strong emotional stimuli on the electroencephalogram of thirty patients with convulsive disorder and nine non-epileptic controls is the subject of this report.

Diagnosis of psychomotor or psychosensory epilepsy was made in twenty-two of the thirty patients and undifferentiated grand mal seizures occur in eight. In the former category are individuals who report psychic aura, visceral aura, automatism, or combinations of these components. Of this group of twenty-two individuals, seventeen manifest abnormal cerebral electrical activity over the temporal regions during routine electroencephalograms or conventional activating procedures (hyperventilation, sleep, Metrazol, flickering light). Two patients demonstrate focal occipital spiking and three show diffuse mixed slow and sharp activity.

The eight patients with grand mal seizures all have warningless tonic-clonic attacks of varying severity, and report never having experienced aura or automatism. Five give electroencephalographic evidence of extra temporal focal spike or slow activity, and three show diffuse spike-wave abnormality. Nine individuals, healthy medical students, served as controls for the epileptic group.

Electroencephalograms were made from all patients and the controls before and during an interview designed to provoke intense emotional responses. The interview was structured in respect to each patient's personal and social background. Patients were interviewed on numerous occasions prior to the stress activation and a strong physician-patient relationship based on long-term management of the convulsive disorder and allied problems obtained in most instances. Additional personal information was obtained from each individual *via* the Minnesota Multiphasic Personality Inventory which, after being completed by the subject, was scrutinized question by question for hints as to areas of particualr psychological difficulty. The patients were maintained on their usual anticonvulsant medication prior to the test. Numerous previous electroencephalograms were available for each patient including sleep and hyperventilation activations in all, and Metrazol or photic activation in many. A control study including hyperventilation was carried out immediately prior to the recording under conditions of experimental psychological stress. Frontal, central, occipital, anterior temporal and basal (nasopharyngeal) electrodes were used. Bipolar and unipolar recordings were made on a Grass Model IIID 8-channel electroencephalograph.

During the stress interview, the investigator directed a series of questions, criticisms, accusations, and finally laudatory comments and apologies to the subject during the recording of the electroencephalogram. These efforts were geared toward maximal emotional response from the subject. Content of the interview was greatly individualized from patient to patient. The following notes from one such interview may serve to illustrate this procedure.

A patient strongly dependent on the investigator, highly motivated to co-

operate under all circumstances, was told during the recording that the present doctor-patient relationship was at an end, and that it would be necessary for the patient to seek other medical counsel, no more help could be offered him, etc. The patient's subjective reaction to this as reported afterward was intense, as he stated, he seemed to be "falling down a well shaft, heart first." A few moments later, the patient was reassured and told that the examiner did not mean what was said, but was only testing his responses, that his problem would always be a foremost one, of great concern, etc. To this the patient smiled, visibly relaxed, and afterward reported "a weight taken off my chest."

Feelings of anger were rather easily provoked by accusing subjects of dishonesty, malingering, or total lack of cooperation.

TABLE 1

*EEG Alterations During Stress; Grand Mal vs. Psychomotor**

	No Significant Change	Normal Responses	Abn. Responses Similar to Pre-Activation E.E.G.	Abn. Responses Not Seen on Routine E.E.G.	Total
	N	*N*	*N*	*N*	
Grand Mal Only	1	4	2	1	8
Psychomotor	4	1	7	10	22
Total	5	5	9	11	30

* Summary of results of electroencephalogram changes during contrived emotional provocation. Note that nearly two-thirds of the patients with undifferentiated grand mal showed no pathological alteration in electroencephalogram during stressful interview while three-quarters of the patients with psychomotor seizures reacted abnormally. Pathological changes not observed on previous tracings accompanied stress in nearly half of the psychomotor group, and in only one patient in the undifferentiated grand mal category.

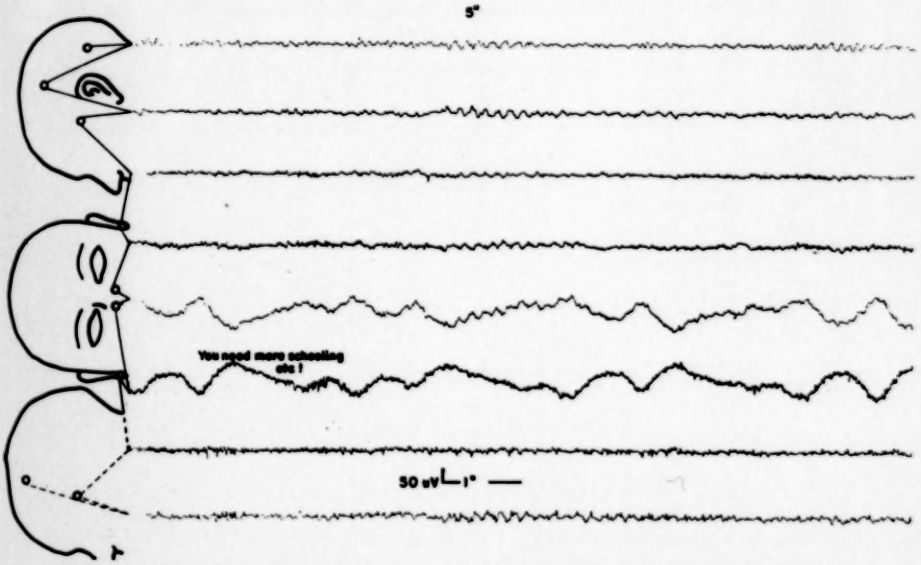

FIG. 1. "Normal" response to emotional stimuli from a 41-year-old lay minister with generalized seizures preceded by terrifying thoughts. Stressful accusations caused considerable anger and were followed by transient rhythmic theta runs from all regions of the head. Similar responses were found in the records from the non-epileptic control group. The very slow sway in channels 5 and 6 is an artifact from the poorly immobilized right nasopharyngeal electrode.

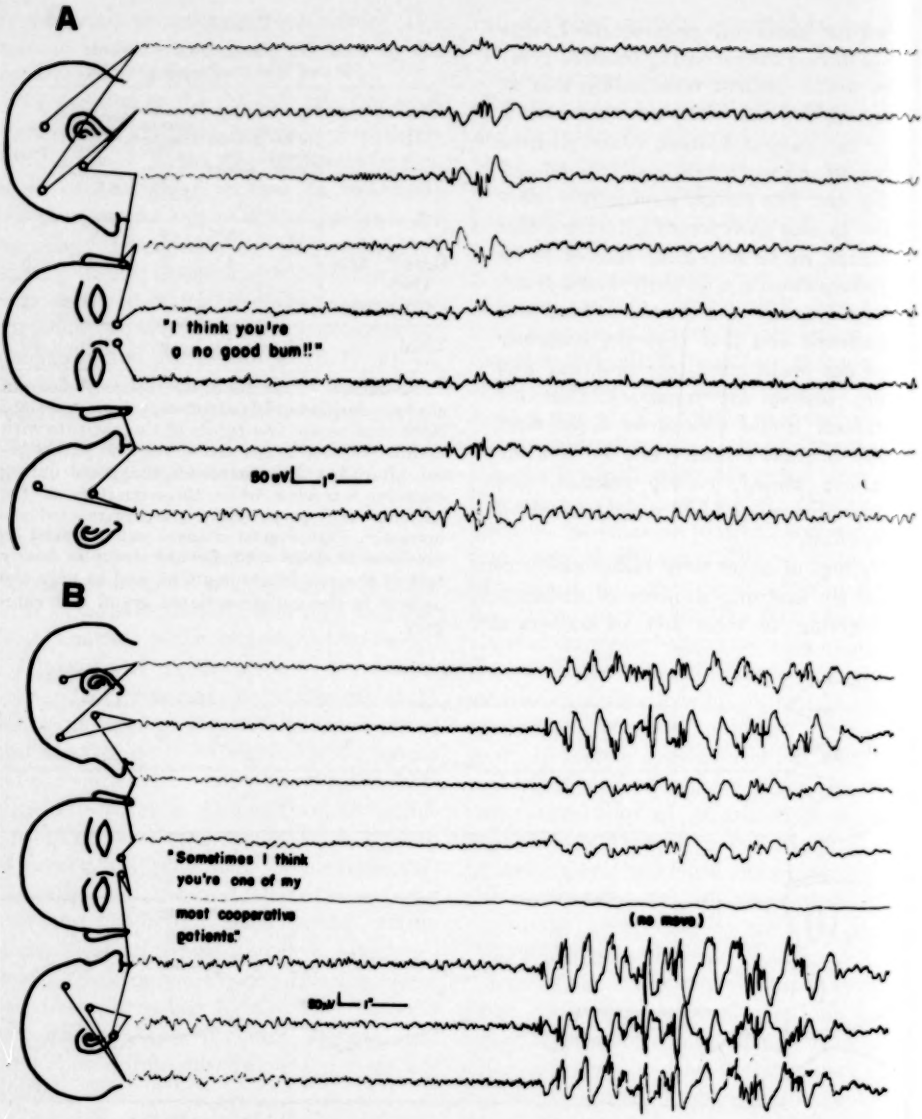

FIG. 2. Twenty-eight year old male with warningless major seizures since childhood. These often occur in a setting of emotional excitation and increased irritability. Previous records have demonstrated bilateral synchronous wave-spike. Two wave-spike paroxysms less than one-half second in duration occurred during the fifteen minute control period preceding the emotional activation. Twenty-four wave-spike complexes occurred during fifteen consecutive minutes of the emotional activation. Five of these paroxysms exceeded five seconds in duration. (A). Response to critical remark. Latency approximately 3½ seconds. No clinical sign. Patient denied subjective change. (B). Response to compliment. Latency approximately 5 seconds. No clinical sign. Patient denied subjective change. (C). Response to "neutral" question. Acceleration and voltage decrement approximately 3½ seconds following statement. No paroxysmal discharge. The inferior temporal region ("visceral brain") is evidently least involved in the discharge in (A) and (B).

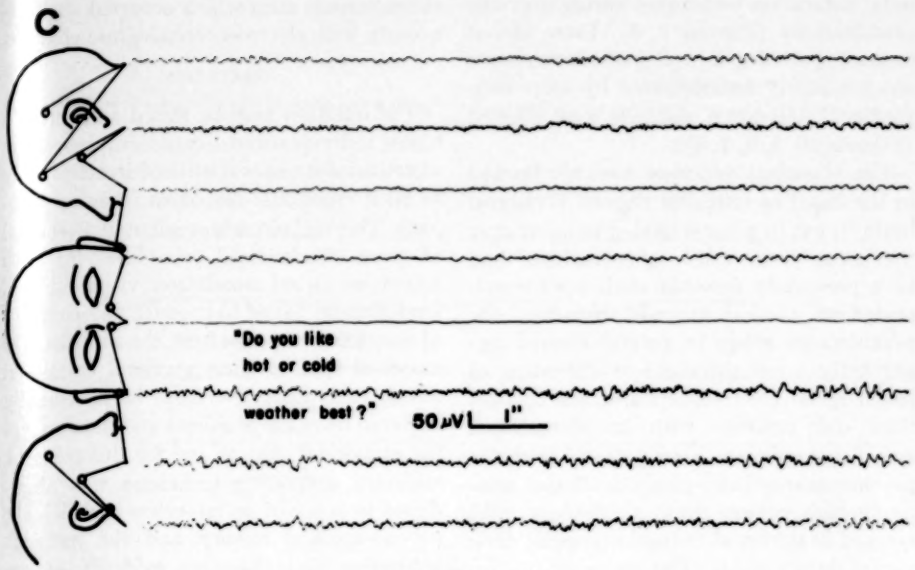

FIG. 2—*Continued*

Moods of sorrow, fear or pleasure were evoked in some instances by the investigator describing in considerable detail and with great feeling the circumstances of past events known to have been emotionally highly significant to the patient. Occasionally the patient's transcribed verbatim description of emotionally provocative events was played back to him during the recording of the electroencephalogram. Sudden disturbances such as an air-blast or cry of "Fire" were used to provoke startle reactions. Responsivity of patients to provocation varies greatly and appears to be related not only to the content of the interview, but to the mood and temperament of both patient and investigator. The warmth of the pre-existing doctor-patient relationship also plays an important role in determining the subject's reaction to such contrived stress.

In sum, during the procedure, an attempt was made to elicit strong feelings of anger, sorrow, embarassment, mirth and pleasure. Not always were these goals achieved.

RESULTS

Table 1 summarizes the results of the observations made.

There is considerable loss of information in attempting to present the results of these studies in tabular form. Certain individuals were decidedly indifferent to all attempts to excite emotional response while others displayed marked lability of emotion and were readily provoked to anger or tears. Hence, interpretation of the figures tabulated in Table 1 relates to the composition of the group as well as to the validity of the method.

No significant change in the electroencephalogram was noted during the stressful interview in five patients. Five individuals responded no differently than the control ("normal") group (Figure 1). Twenty patients demonstrated abnormal electroencephalogram alterations in response to the psychological stress. Of this number, nine showed clear-cut exaggeration of spiking or paroxysmal activity of similar nature to that obtained with routine studies or with

usual activation techniques during previous examinations (Figures 2, 3). From eleven patients, pathological epileptiform responses not previously demonstrated by more conventional activation methods were elicited (Figures 4b, 5, 6, 7, 8).

The abnormal responses were not limited to the basal or temporal regions ("visceral brain"), but in general tended to occur over the areas from which abnormalities had been previously demonstrated or were suspected on clinical grounds. However, the psychomotor group in general showed significantly lower threshold to elicitation of pathological electroencephalogram changes than did patients with undifferentiated grand mal epilepsy. Four patients from the psychomotor-sensory group developed relatively high voltage rhythmic activity most marked in the basal (nasopharyngeal) derivation during stress (Figures 4a, 9).

Among the nine "normal" controls, no pathological electroencephalogram changes were observed during stress and basal activity remained low voltage rapid in character. Alpha blocking, transient frontal, or frontotemporal theta, and exaggeration of alpha amplitude were the only detectable alterations in the record during emotional excitation.

Despite the obvious interpersonal problems arising during such a study, no patients objected to having been subjected to the stress interview when the purposes of the investigation were explained at the conclusion of the test period. Indeed, many expressed gratitude for the added interest shown in their problem. An obvious difficulty with this technique is that it is not possible to repeat the interview a number of times under identical circumstances. During repeat sessions, patients are typically less responsive and more sophisticated about the procedure, although in a few instances emotional lability was maintained or even increased during successive trials. Only one individual suffered a frank seizure during the interview, and two patients reported characteristic aura which occurred simultaneously with electroencephalogram changes.

DISCUSSION

The question may be raised as to why a highly individualized, nonuniform procedure of artificial stress was utilized in attempting to elicit emotional responses from our subjects. This technique was adopted after trial of more standardized procedures for such activation (word association, visual stimuli, loud sounds) failed to produce any equality of emotional response from the subjects. We reasoned that to elicit maximal emotional affect, each interview must be specifically centered upon the problems and pleasures of the individual subject and for this reason a standard activating technique was abandoned in favor of an interview in which the psycho-medical history and the patient's subjective and objective evidence of enhanced emotional affect were our principal subjective guides in directing the content of the interview.

Changes in the electroencephalogram of non-epileptic individuals when subjected to emotional stress have been described by numerous investigtaors and include alpha blocking responses with generalized flattening (desynchronization) of the electroencephalogram and appearance of relatively slow activity, usually in the theta range, of variable latency and duration, and with a rather diffuse distribution over the scalp when recording by usual methods (27). The basal electroencephalogram (obtained with nasopharyngeal leads and monitoring inferior and medial temporal lobe) of normal or anxious individuals under stress shows similar changes (5). Elicitation of slow activity from the occipital region of the scalp and basal cerebrum (sphenoperiosteal derivation) has been reported in normal and psychotic patients experimentally stressed by psychological means (11, 13). The results from our control group are entirely compatible with these observations.

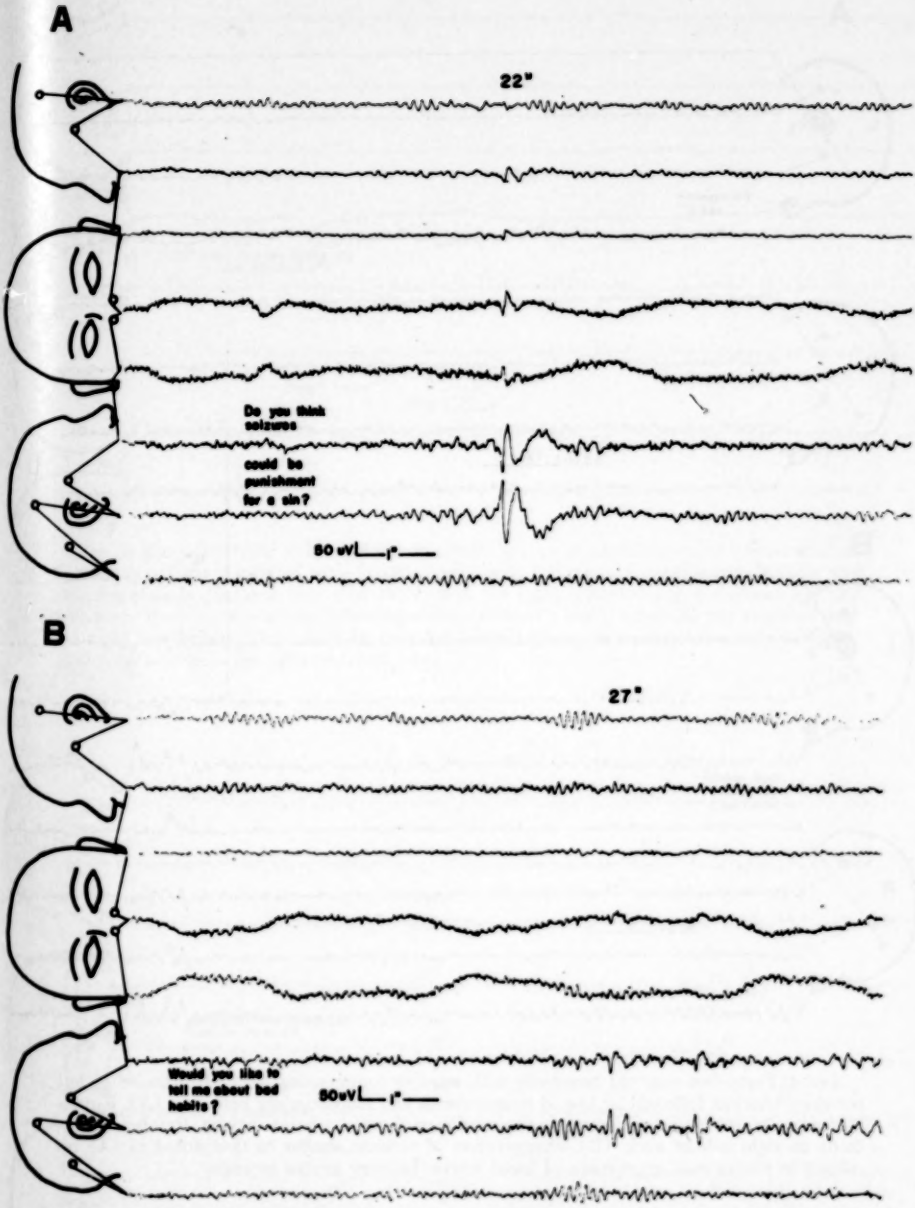

FIG. 3. Thirty-four year old accountant with long history of psychic seizures characterized by feeling of strangeness, loss of contact, inappropriate speech and automatism. Numerous previous waking records within normal limits. Sleep and metrazol activations demonstrate right anterior temporal spiking similar to that induced with stress illustrated above. (A). Spike discharge across basal girdle of electrodes, maximum at the right anterior temporal derivation. (B). Interviewer's question was followed by brief aura preceding the right anterior temporal spikes.

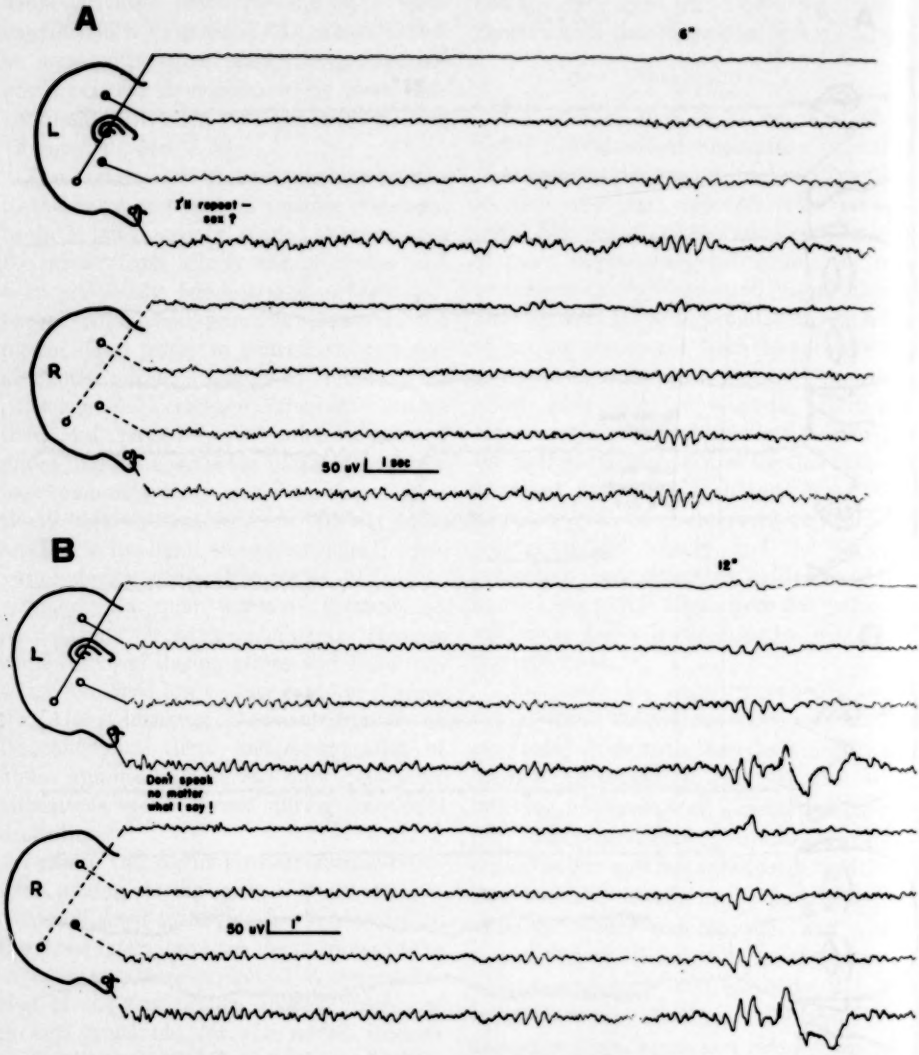

FIG. 4. Forty-two year old housewife with seizures commencing with paresthesiae of left posterior pharynx followed by loss of consciousness and inappropriate behavior. (A). Rhythmic six to seven cycle per second waves maximum from the basal regions. Reference electrode on right side of neck. (B). Exaggeration of activity similar to that noted in (A) resulting in paroxysmal appearance of basal waves. Latency twelve seconds.

Precipitation of convulsions in epileptic individuals during emotional conflict and stress has been reported by Barker (2, 3), Aring *et al.* (1) and others. Barker suggests that the "epileptic reaction may be used by a neurosis to discharge masses of energy," and discerns unconscious conflictful motives hidden beneath apparently neutral circumstances surrounding a seizure. It may be of value to include this concept in a wider statement of the problem of epilepsy: namely, does the epileptic seizure

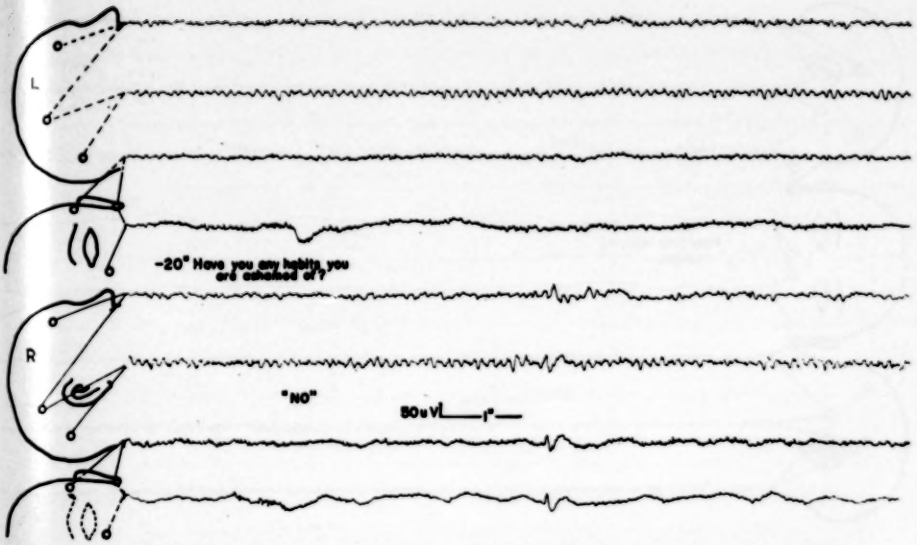

FIG. 5. Forty-four year old lumber worker with history of recent repeated pleasurable olfactory sensations associated with flashing light, twice followed by convulsions. Waking and sleeping records disclosed only slow activity in the right temporal region (channels 7 and 8 above). Twenty-two seconds following above question a sharp potential was recorded over the right hemisphere. This could be repeated several times. Temporal lobectomy disclosed glial proliferation in the right temporal lobe.

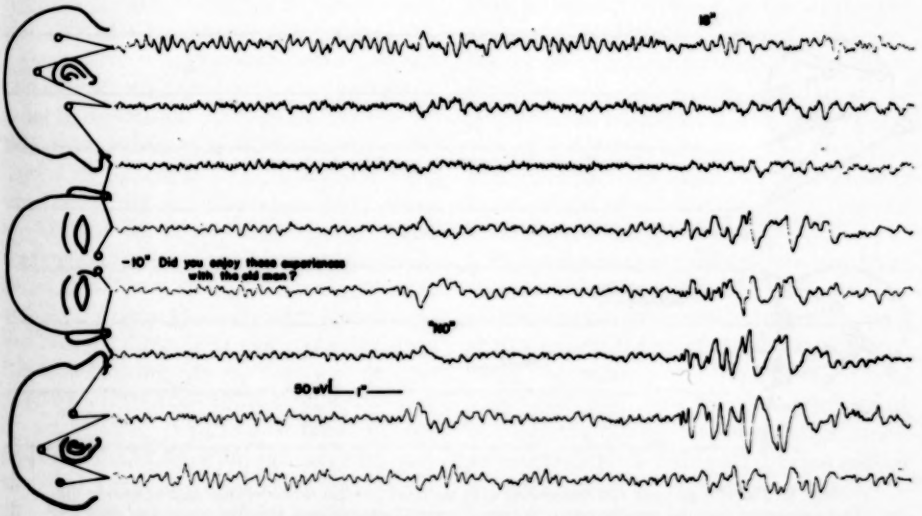

FIG. 6. Seventeen year old girl with history of major and minor seizures since age seven. Attacks commence with giddiness, hallucinations of color, head and eyes to left, automatic activity occasionally followed by major seizure. High voltage polyspike-wave discharges over right fronto-temporal region were regularly precipitated by emotionally charged stimuli.

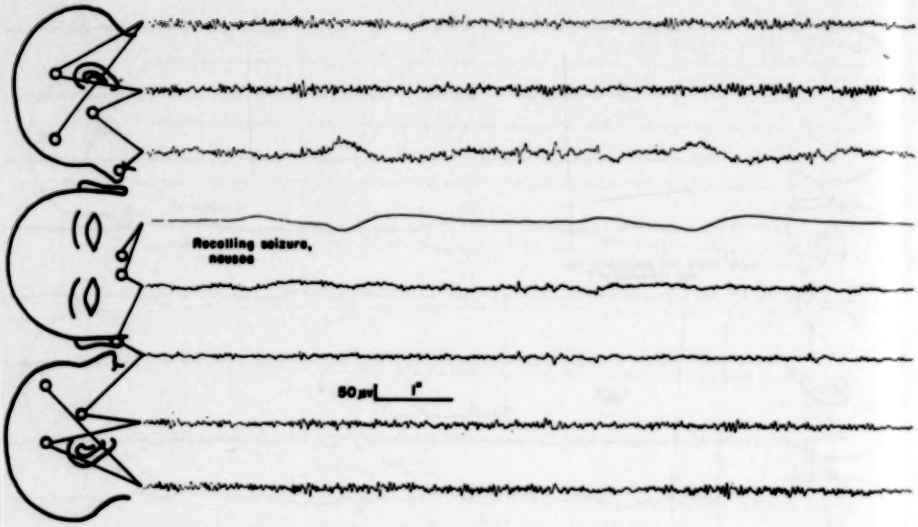

FIG. 7. Thirty year old man with generalized seizures since age six which occur frequently under emotional stress. Abdominal aura occurs prior to attacks and frequently patient experiences repeated aura (gastric "rising" sensation) over periods of hours. Numerous previous EEGs, including metrazol and sleep studies demonstrate only diffuse low voltage rapid activity. Small nasopharyngeal spikes were recorded during the stress interview. Above, patient is being reminded of the feeling of dread which accompanies the abdominal aura.

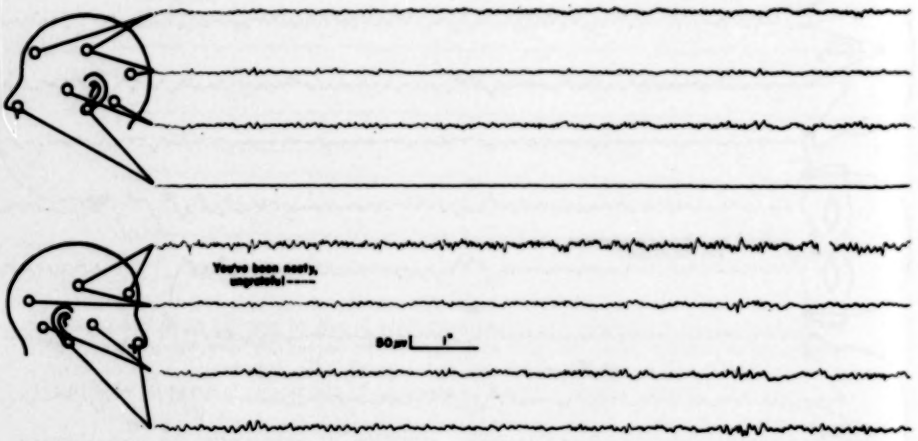

FIG. 8. Thirty-one year old housewife with marked paranoid tendencies and behavior disturbance who has had psychomotor automatism and generalized seizures since age thirteen. Previous electroencephalograms disclosed no specific abnormalities. Emotional stress was followed by low voltage sharp activity over the right hemisphere reversing in sign at the anterior temporal derivation.

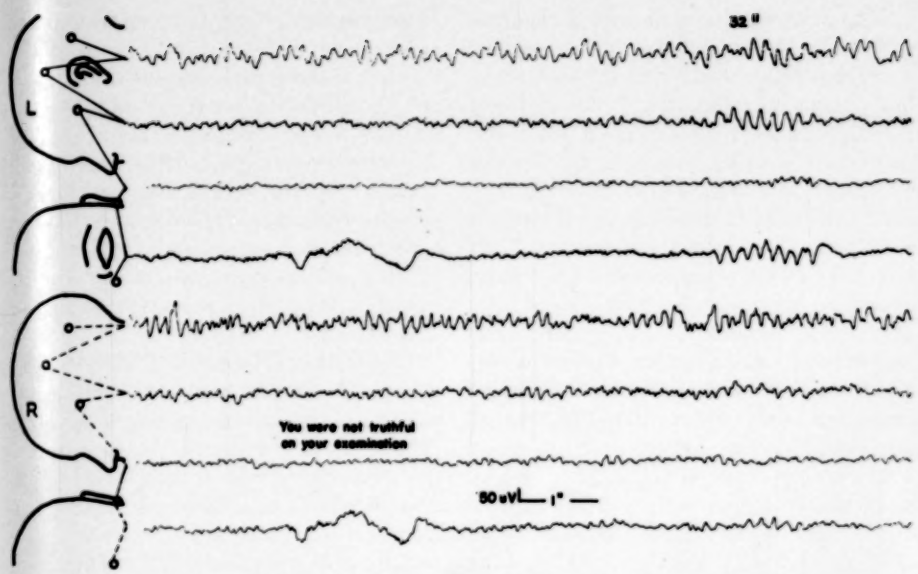

FIG. 9. Nineteen year old female with adversive seizures and automatism since age ten preceded by "scary" feeling as though someone is going to grab her. Attacks often occur when intensely excited. Mild right hemiparesis and hemianopia present. Previous records disclose random slow activity in the posterior left hemisphere. Emotional perturbation is followed by rhythmic 5 to 6 cycle per second activity over the left temporal and nasopharyngeal regions. No spiking was elicited.

signify a stimulus-response sequence which may play an adaptive role in behavior?

Convulsive behavior which occurs in certain animals suggests that such a possibility is not unreasonable. Audiogenic seizures occurring in a number of rodents reared in the laboratory appear as an alternative to flight when naturally sought escape mechanisms are blocked. M. R. A. Chance has proposed that such convulsive behavior may be established as a "fixed alternative consummating activity" within the hierarchy of behavior to which the flight drive can give expression. Running-barking fits of dogs are precipitated by startle and confusion and enhanced by non-specific emotional stimuli. Chance proposes that in the wild, such activity may have had a protective role, and that the canine fit may be a vestigial adaptive stereotype precipitated under a variety of conditions (4). Lindsley *et al.* (20) have shown that audiogenic seizures in the susceptible rat can be inhibited if "substitute behavior" (ear or nose rubbing, teeth chattering, chewing, shivering, etc.) occurs, or if the animal is restrained, immobilized by curare, or previously subjected to vagotomy. The latter procedure prevents heart rate alterations to the stimulus which were invariably present in animals which convulsed.

These observations point to the possibility that the seizure may act as a "release" pathway for central hyperexcitability when usual energy outlets for relief are absent. Furthermore, the participation of both peripheral autonomic and somatic neural relays in building the central excitatory state to seizure threshold is indicated by the seizure blocking effects of vagotomy and curare.

Further evidence of the importance of input factors in triggering epileptiform behavior in the predisposed comes from obser-

vations of animals experimentally rendered chronically epileptic. Convulsive seizures secondary to destructive or irritative cerebral lesions in monkey and rat are most reliably triggered by contrived emotional excitement (teasing, prodding, etc.) (18) or by peripheral stimuli such as flickering light, rhythmic clicks or stroking, particularly if the stimulus occurs as a surprise (9). Murphy and Gellhorn demonstrated facilitation of cortical motor discharge during and after electrical stimulation of the hypothalamus and proposed that epileptic seizures occurring during stress may depend upon primary activation of this region (23). Epileptiform responses to stress recorded from amygdala (10) and hippocampal region (22) in man and animals suggest that emotional provocation may initiate focal abnormality in these regions of a "reflex epilepsy" type as proposed by Liberson (19).

The relatively long and variable latency between stressful stimulus and EEG change (4–30 seconds) in our group of patients does not suggest a "reflex" activation of focal hyperirritable tissue. Emotional change is frequently followed by rhythmic slow patterns in the EEG (the "theta" response described by Grey Walter, 27) which may sum with those slow characteristics already present in the interseizure electroencephalogram and augment the tendency to paroxysmal discharge.

Comprehension of the anatomical and physiological basis of such responses awaits further investigation of the complex interconnections between rhinencephalon, hypothalamus and widely dispersed cortical and subcortical structures.

SUMMARY

The effect of emotional stress on the electroencephalograms of thirty patients with epilepsy and nine "normal" controls has been studied. It has been possible to precipitate previously unobtained epileptiform abnormalities in the electroencephalograms of one-third of a group of patients with convulsive disorders and to reduplicate or exaggerate previously demonstrated pathological electroencephalogram changes in another third. The small control group fails to show similar changes. EEGs of the psychomotor-sensory group were more readily activated by this method than were those of patients with other types of seizure. Changes tend to appear over the cerebral areas in which abnormal electrical activity was obtained during prior examinations or was anticipated on clinical grounds.

This technique is reported less to suggest a useful means of activating the electroencephalogram in the epileptic than to emphasize the importance of input factors in precipitating convulsive activity in the predisposed. In certain instances at least, epileptiform discharges may represent faulty circuiting of responses to external stimuli, related to underlying anatomical defects.

REFERENCES

1. Aring, C. D., Lederer, H. D. and Rosenbaum, M. The role of emotion in the causation of epilepsy. A. Res. Nerv. & Ment. Dis., Proc., **26**: 561–572, 1947.
2. Barker, W. Studies on epilepsy: The petit mal attack as a response within the central nervous system to distress in organism-environmental integration. Psychosom. Med., **10**: 73–94, 1948.
3. Barker, W. and Barker, S. Experimental production of human convulsive brain potentials by stress induced effects upon neural integrative function: Dynamics of the convulsive reaction to stress. A. Res. Nerv. & Ment. Dis., Proc., **29**: 90–113, 1950.
4. Chance, M. R. A. Role of convulsions in behavior. Behavioral Sci., **2**: 30–45, 1957.
5. Faure, J. Au suject de l'activité de la base du cerveau dans l'anxiété (dérivation basale). Rev. neurol., **80**: 621–623, 1948.
6. Gastaut, H., Naquet, R., Vigoroux, R. and Corriol, J. Provocation de comportments émotionnels divers par stimulation rhinencephalique chez le chat avec electrodes a demeure. Rev. neurol., **86**: 319–327, 1952.
7. Gibbs, E. L., Gibbs, F. A. and Fuster, B. Psychomotor epilepsy. Arch. Neurol. & Psychiat., **50**: 331–339, 1948.
8. Gowers, W. R. *The Borderland of Epilepsy.* J. & A. Churchill, Ltd., London, 1907.
9. Green, J. D., Clemente, C. D. and deGroot, J. Experimentally induced epilepsy in the cat with injury of Cornu Ammonis. A. M. A. Arch. Neurol. & Psychiat., **78**: 259–263, 1957.

10. Groethuysen, V. C., Robinson, D. B., Haylett, C. H., Estes, H. R. and Johnson, A. M. Depth electrographic recording of a seizure during a structured interview. Psychosom. Med., **19**: 353–362, 1957.
11. Grinker, R. R. and Serota, H. Studies on corticohypothalamic relationships in cat and man. J. Neurophysiol., **1**: 573–589, 1938.
12. Herpin, T. *Du pronostic et du traitement curatif de l'épilepsie*. J. B. Bailliere, Paris, 1852.
13. Hoagland, H., Cameron, D. E. and Rubin, M. A. Emotion in man as tested by the delta index of the electroencephalogram. J. Gen. Psychol., **19**: 227–245, 1938.
14. Jackson, J. H. *Selected Writings of John Hughlings Jackson*. Hodder and Stoughton, Ltd., London, 1931.
15. Jasper, H. H. Electrical signs of epileptic discharge. Electroencephalog. & Clin. Neurophysiol., **1**: 11–18, 1949.
16. Kaada, B. R. Somatomotor, autonomic and electrocorticographic responses to electrical stimulation of "rhinencephalic" and other structures in primates, cat and dog. Acta physiol. scandinav., **24**: Suppl. 83, 1–285, 1951.
17. Kluver, H. and Bucy, P. C. "Psychic blindness" and other symptoms following bilateral temporal lobectomy in rhesus monkeys. Am. J. Physiol., **119**: 352–353, 1937.
18. Kopeloff, L. M., Barrera, S. E. and Kopeloff, N. Recurrent convulsive seizures in animals produced by immunologic and chemical means. Am. J. Psychiat., **98**: 881–902, 1942.
19. Liberson, W. T. Emotional and psychological factors in epilepsy: Psychological background. Am. J. Psychiat., **112**: 91–106, 1955.
20. Lindsley, D. B., Finger, F. W. and Henry, C. E. Some physiological aspects of audiogenic seizures in rats. J. Neurophysiol., **5**: 185–198, 1942.
21. MacLean, P. D. Some psychiatric implications of physiological studies on the fronto-temporal portion of the limbic system (visceral brain). Electroencephalog. & Clin. Neurophysiol., **4**: 407–418, 1952.
22. MacLean, P. D., Horwitz, N. H. and Robinson, F. Olfactory-like responses in pyriform area to non-olfactory stimulation. Yale J. Biol. & Med., **25**: 159–172, 1952.
23. Murphy, J. P. and Gellhorn, E. The influence of hypothalamic stimulation on cortically induced movements and on action potentials of the cortex. J. Neurophysiol., **8**: 341–364, 1945.
24. Papez, J. A proposed mechanism of emotion. Arch. Neurol. & Psychiat., **38**: 725–743, 1937.
25. Penfield, W. and Jasper, H. H. *Epilepsy and the Functional Anatomy of the Human Brain*. Little, Brown and Co., Boston, 1954.
26. Schreiner, L. and Kling, A. Rhinencephalon and behavior. Am. J. Physiol., **184**: 486–490, 1956.
27. Walter, V. J. and Walter, W. G. Central effects of rhythmic sensory stimulation. Electroencephalog. & Clin. Neurophysiol., **1**: 57–86, 1949.

SERUM MAGNESIUM IN DELIRIUM TREMENS AND ALCOHOLIC HALLUCINOSIS[1]

JACK MENDELSON, M.D.,[2] DONALD WEXLER, M.D.,[2] PHILIP KUBZANSKY, PH.D.,[2] P. HERBERT LEIDERMAN, M.D.[2] AND PHILIP SOLOMON, M.D.[2]

INTRODUCTION

The relationship of serum magnesium levels to alcohol withdrawal symptoms is not clearly understood. Flink and his associates (9) studied a group of alcoholic patients with a variety of symptoms ranging from "impending delirium tremens" to "severe delirium tremens." Their findings indicated that there was a statistically significant difference of serum magnesium levels between the alcoholic patients and the normals seen in their laboratory. It appeared that patients who had the most severe symptoms of tremor and delirium had the lowest serum magnesium values. Flink and his associates (8) also reported favorable therapeutic results with patients suffering from delirium tremens following intramuscular administration of magnesium sulphate in dosages which were not considered to be hypnotic. Suter and Klingman (22) confirmed Flink's findings of low serum magnesium levels in delirium tremens and in a variety of other alcoholic withdrawal symptoms. They too reported a favorable clinical response to magnesium sulphate therapy. These studies, and the reports of other authors of successful therapy with cases of delirium tremens treated empirically with magnesium sulphate (4, 18), suggested a further investigation of the relationship between serum magnesium levels, delirium tremens, and other alcohol withdrawal symptoms.

PROCEDURE

Fifty alcoholic patients and eighteen control patients were the subjects of this study. All patients were admitted to the Boston City Hospital or to the Massachusetts General Hospital. The alcoholic patients were adult white males between the ages of 23 and 55 years. The average age was 39 for patients with delirium tremens and 36 for patients with alcoholic hallucinosis. It has been shown that hypomagnesemia may be present in patients with decompensated hepatic cirrhosis (20). Therefore all patients who had ascites, icterus, or abnormal BSP levels were not included in this series. Patients with pulmonary, cardiac or renal disease were also eliminated. The eighteen control patients were convalescing tuberculosis patients whose disease was in remission and psychiatric ward patients who had symptoms of psychoneurosis without evidence of psychosis or organic disease. They were adult males between the ages of 20 and 55 years and came from essentially the same socioeconomic background as the alcoholic patients. All control patients were on a hospital diet for at least two weeks. None of the control patients was febrile, dehydrated, or showed any evidence of dietary or electrolyte abnormalities.

There were two groups of alcoholic patients:

1) Thirty patients had delirium tremens. These were chronic alcoholic patients ad-

[1] This study was supported in part by a research grant (M 1955) from the National Institute of Mental Health, Public Health Service, and a grant from the Warner-Chilcott Chemical Co., Morris Plains, New Jersey.

[2] The Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, and the Psychiatric Research Laboratory, Boston City Hospital; Department of Neurology and Psychiatry, Harvard Medical School. The authors wish to thank the Statistical Consultation Service, Harvard Medical School and Gene M. Smith. Ph.D. of the Dept. of Anesthesia, Massachusetts General Hospital for their assistance with the statistical evaluation of the data.

mitted after an episode of prolonged ingestion of intoxicating beverages and subsequent withdrawal. They all had symptoms of delirium, disorientation, gross psychomotor agitation, tremors or convulsions, hyperhydrosis, and delusions.

2) Twenty patients had alcoholic hallucinosis. These patients were chronic alcoholics, admitted after a prolonged period of ingestion of alcoholic beverages, followed by a period of withdrawal. They had symptoms of hallucinosis, mild psychomotor agitation and usually a mild tremor. They were, however, oriented, and did not show evidence of gross psychomotor agitation or convulsions.

Serum was obtained from all patients shortly after admission to the hospital. Serum magnesium was determined by a method described by Garner (10) in which magnesium is precipitated as the hydroxide of an octidine sulfo-dye, titan yellow. Gum ghatti is used to maintain a dispersion of the magnesium-dye lake. Standard solutions of magnesium sulfate in 1 and 2 m Eq/l concentration were freshly prepared daily and run prior to and following each series of experimental determinations. Duplicate series of control and experimental determinations did not differ in any instance more than ±0.1 m Eq/l.

RESULTS

Group data are presented in Table 1. Patients who had delirium tremens had the lowest serum magnesium levels, while those with alcoholic hallucinosis had lower values than controls, but higher values than patients with delirium tremens.

A nonparametric method of analysis, the Mann-Whitney *U* test (19) was used in the statistical evaluation of the data. This test was chosen because the assumption of normal distribution of serum magnesium values required by the parametric *t* test could not be made. This statistical analysis showed that mean serum magnesium value of the three groups differed from each other significantly (Table 2).

TABLE 1

Serum Magnesium Levels: Group Data

	N	Mean mEq/l	Standard Deviation	Standard Error
Controls	18	1.8	0.17	0.04
Alcoholic hallucinosis	20	1.6	0.34	0.08
Delirium tremens	30	1.4	0.38	0.07

TABLE 2

Significance of Differences of Serum Magnesium Levels: Mann-Whitney U Test

	P
Controls vs. Alcoholic Hallucinosis	0.037
Controls vs. Delirium Tremens	0.001
Alcoholic Hallucinosis vs. Delirium tremens	0.038

The distribution of serum magnesium values by groups is shown in Figure 1. In comparing the variance of the three groups by the *F* test (5), the controls differ significantly from the two alcoholic groups (Table 3). There were no significant differences in variability between the delirium tremens group and the hallucinosis group.

Within the group of thirty patients with delirium tremens, seven were studied during the acute and convalescent phases of their illness (Table 4). None of these patients was given magnesium during the course of treatment. The mean value for serum magnesium during the acute phase of delirium tremens was 1.4 m Eq/l. Regardless of the initial level of serum magnesium concentration, a rise was found in every case following cessation of symptoms. When tested with a Wilcoxon matched-pairs signed-ranks test (19), this difference was found to be significant at the .01 level of confidence. This nonparametric test was used because the assumption of normal distribution of serum magnesium values could not be made.

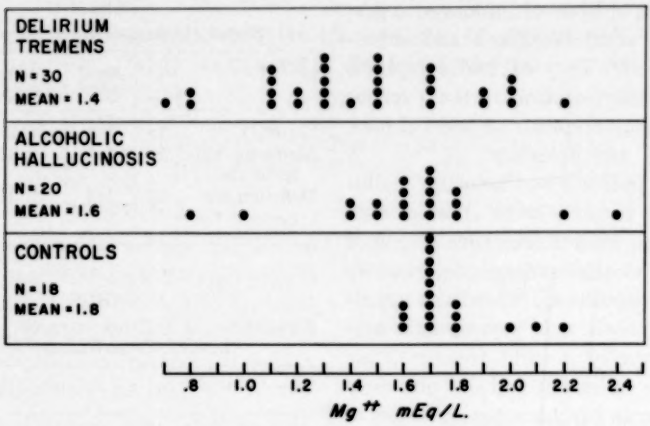

FIG. 1. Serum Magnesium Levels

TABLE 3

Variability of Distribution of Serum Magnesium Levels: F Test

	F	P
Controls vs. Alcoholic hallucinosis	4.20	<0.005
Controls vs. Delirium Tremens	5.22	<0.005
Alcoholic Hallucinosis vs. Delirium Tremens	1.24	N.S.

TABLE 4

Serum Magnesium Levels (mEq/l), Delirium Tremens: Wilcoxon Matched-Pairs Signed-Ranks Test

Case	Acute Values	Convalescent Values	Differences*
1	1.9	2.3	+0.4
2	2.0	2.2	+0.2
3	1.5	1.9	+0.4
4	1.7	1.9	+0.2
5	0.7	1.4	+0.7
6	1.1	1.6	+0.5
7	1.3	1.5	+0.2

* All differences at $p < 0.01$.

DISCUSSION

The findings of this study support the observations of Flink and his associates, and those of Suter and Klingman, in that there is a decreased concentration of serum magnesium in patients with delirium tremens and alcoholic hallucinosis. However, we have a number of reservations concerning the relationship. It should be emphasized that both delirium tremens and alcoholic hallucinosis are not disease entities, but congeries of symptoms which vary in frequency and intensity in a given individual. It is not uncommon for patients to exhibit fluctuating degrees of delirium, tremulousness and agitation with spontaneous patterns of remission and exacerbation during the course of their illness. The variability of these symptoms has been pointed out by Victor and Adams (23). Our patients with delirium tremens and alcoholic hallucinosis showed greater variance in serum magnesium concentration than controls.

An interesting factor for consideration is that patients with alcohol withdrawal symptoms usually have increased autonomic activity, including moderate to severe hyperhydrosis. Studies (25) have shown that sweat contains an extremely high concentration of magnesium (5 m Eq/l); therefore severe sweating in patients with delirium tremens may be a significant factor affecting their serum magnesium concentration. Whether a serum magnesium deficit results from, or is the cause of delirium, increased psychomotor agitation, disorientation, hyperhydrosis and hallucinosis remains to be determined. At the present stage of knowl-

edge no direct causal relationships can be inferred. The finding of decreased serum magnesium in alcoholic withdrawal states supports only an associational relationship.

A word should be said about the method of analysis employed for the determination of magnesium, in serum and tissues. The normal values in this study are in agreement with those published by Flink and his associates (1.91 ± 0.20 m Eq/l), Suter and Klingman (1.9 m Eq/l), and normal values reported by a number of other investigators (12, 17, 20, 26). However, Wacker and Vallee (24) point out that the chemical methods for magnesium analysis currently used are difficult, variable and inaccurate. They suggest that flame photometric techniques yield more reliable results.

What are some possible physiological and biochemical mechanisms through which low serum magnesium levels may be related to alcohol withdrawal states? In order to clarify these mechanisms, more information is necessary concerning the relationship between intracellular and extracellular magnesium balance. Klingman and his associates (14) have found, in animals on magnesium-deficient diets which produce decreased serum magnesium levels, that intracellular magnesium levels in the brain may remain unchanged, or may even increase. Thus, as in the measurement of potassium, extracellular measurement of magnesium may not give an adequate indication of changes within the cell itself.

A number of authors have speculated on the role of magnesium deficit in tremors and convulsions. It is difficult to make interpretations of abnormalities of neuromuscular function, based upon assumptions of the relationship of magnesium concentration to acetylcholine release and utilization at the neuromuscular junction. With regard to acetylcholine utilization, it has been demonstrated (2) that the effects of magnesium at the neuromuscular junction cannot be interpreted in terms of a blocking effect similar to that produced by curare. Both calcium and magnesium appear to behave as activators of the quantal ejection mechanism of acetylcholine, but not to enter directly into this mechanism *per se*. These same considerations are necessary for assessing the action of magnesium upon presynaptic acetylcholine release, as occurs, for example, in sympathetic ganglia (13).

The hypothesis that a magnesium deficiency exists in alcoholic patients who have consumed copious amounts of alcoholic beverages and have had a poor or restricted diet, is as yet unsubstantiated. It has been shown (21) that starvation for a period as long as forty-five days may not affect serum magnesium concentration appreciably. The mechanism regulating body mobilization of magnesium from a variety of metabolic pools during prolonged periods of dietary deficit is not well understood (7). Barnes and his associates (1) have demonstrated the great efficiency of the human body in conserving magnesium during periods of dietary magnesium deficit. It appears that magnesium, like sodium and unlike potassium, can be "rigidly conserved in the presence of a specific deficiency," though the mechanism whereby this occurs remains to be determined. In the present study, an elevation of serum magnesium concentration occurred, without administration of supplementary magnesium, in the groups of patients with delirium tremens who were observed in the acute and convalescent phases of their illness.

There has been much speculation concerning the effects of magnesium deficit upon the numerous enzymatic and metabolic functions which are magnesium-dependent (15, 27). Flink and his associates (8) have emphasized the importance of magnesium in ATP synthesis and utilization. It appears unlikely, however, that the degree of magnesium deficiency observed in studies of extracellular ion content would significantly alter such processes in the central nervous system. The concentration of magnesium in the brain is in excess of the amount which

is optimally required for the activation of enzyme systems involved in carbohydrate degradation (16). The brain contains approximately 11 m Eq of magnesium per kg. of tissue, or 30 m Eq per kg. of cell water. However, a magnesium concentration of 5–10 m Eq/l had been reported (3) to produce maximal activation of highly purified brain phosphatase. There is some evidence (6) suggesting that magnesium excess may affect levels of ATP in brain, but similar findings have been reported for a variety of anesthetic and narcotic agents (11).

Clarification of the role of magnesium in alcoholic withdrawal states awaits further knowledge of the basic physiology and pathophysiology of magnesium.

SUMMARY

Serum magnesium was studied in 30 patients with delirium tremens, 20 patients with alcoholic hallucinosis, and 18 controls. Group values were significantly low in alcoholic hallucinosis and still lower in delirium tremens. Individual values had a narrow distribution in the controls and a significantly wider distribution in alcoholic hallucinosis and delirium tremens. Seven of the delirium tremens patients were studied during convalescence; the value of serum magnesium increased in each without the use of magnesium in the therapy.

These findings are discussed in relationship to the literature on magnesium in alcoholic withdrawal states and to the role of magnesium in physiological processes.

REFERENCES

1. Barnes, B., Cope, O. and Harrison, T. Magnesium conservation in the human being on a low magnesium diet. J. Clin. Inves., **37**: 430–440, 1958.
2. Brink, F. The role of calcium ions in neural processes. Pharmacol. Rev., **6**: 243–298, 1954.
3. Brinkley, F. and Olsen, C. K. Phosphatase of brain tissue. J. Biol. Chem., **186**: 725–730, 1950.
4. Delmas-Marsalet, Lafon and Faure. Traitement du delirium tremens par le sulfate de magnesie intraveineux. Rev. Neurol., **73**: 598–600, 1941.
5. Dixon, W. J. and Massey, F. J. *Introduction to Statistical Analysis.* McGraw-Hill, New York, 1951.
6. DuBois, K. P., Albaum, H. O. and Potter, V. R. Adenosinetriphosphate in magnesium anesthesia. J. Biol. Chem., **147**: 699–704, 1943.
7. Elkington, J. R. and Danowski, T. S. *The Body Fluids.* The Williams & Wilkins Co., Baltimore, 1954.
8. Flink, E. B., McCollister, R., Prasad, A. S., Melby, J. C. and Doe, R. P. Evidences for clinical magnesium deficiency. Ann. Int. Med., **47**: 956–968, 1957.
9. Flink, E. B., Stutzman, F. L., Anderson, A. R., Lonig, T., and Fraser, R. Magnesium deficiency after prolonged parenteral fluid administration and after chronic alcoholism complicated by delirium tremens. J. Lab. and Clin. Med., **43**: 169–183, 1954.
10. Garner, R. J. Colorimetric determination of magnesium in plasma or serum by means of titan yellow. Biochem. J. **40**: 828–831, 1946.
11. Grenell, R. G., Mendelson, J. H. and McElroy, W. D. Biochemical change during cerebral excitation and depression. Trans. Amer. Neurol. Assoc., 95–99, 1955.
12. Hoffman, W. S. Colorimetric method for the determination of serum magnesium based on the hydroxyquinoline precipitation. J. Biol. Chem., **118**: 37–45, 1937.
13. Hutter, O. F. and Kostial, K. Effect of magnesium and calcium ions on the release of acetylcholine. J. Physiol., **124**: 234–241, 1954.
14. Klingman, W. C., Suter, C., Green, R. and Robinson, I. Role of alcoholism and magnesium deficiency in convulsions. Trans. Amer. Neurol. Assoc., 162–165, 1955.
15. Lehninger, A. L. Role of metal ions in enzyme systems. Physiol. Rev., **30**: 393–429, 1950.
16. Manery, J. F. Inorganic metabolism of the brain. Chapter 10 in *The Biology of Mental Health and Disease.* Paul Hoeber Inc., New York, 1955.
17. Orange, M. and Rhein, H. C. Microcetimation of magnesium in body fluids. J. Biol. Chem., **189**: 379–386, 1951.
18. Rosetti, F. Il solfato di magnesio nelle siciosi alcooliche. Rass. Studi psichiatrici, **40**: 272–277, 1951.
19. Siegel, S. *Nonparametric Statistics for the Behavioral Sciences.* McGraw Hill, New York, 1956.
20. Stutzman, F. L., and Amatuzio, D. S. Blood serum magnesium in portal cirrhosis and diabetes mellitus. J. Lab. Clin. Med., **41**: 215–219, 1953.
21. Sunderman, F. W. Studies in serum electrolytes, XIV. Changes in blood and body fluids in prolonged fasting. Am. J. Clin. Path., **17**: 169–180, 1957.

22. Suter, C. and Klingman, W. Neurologic manifestations of magnesium depletion states. Neurology, **4**: 691–699, 1955.
23. Victor, M. and Adams, R. D. The effect of alcohol on the nervous system. Proc. Assoc. Res. Nerv and Ment. Dis, **22**: 526–573, 1953.
24. Wacker, W. E. C. and Vallee, B. L. A study of magnesium metabolism in acute renal failure employing a multi-channel flame spectometer. N. E. J. Med., **257**: 1254–1262, 1957.
25. Walker, B. S., Boyd, W. C. and Asimov, I. *Biochemistry and Human Metabolism*. Williams & Wilkins Co., Baltimore, 1957.
26. Walker, B. S. and Walker, E. W. Normal magnesium metabolism and its significant disturbances. J. Lab. and Clin. Med., **21**: 713–720, 1936.
27. White, A., Handler, P., Smith, E. L. and Stetten, DeW., Jr. *Principles of Biochemistry*. McGraw Hill, New York, 1954.

THE EFFECTS OF CHLORPROMAZINE UPON PSYCHOMOTOR AND PSYCHIATRIC BEHAVIOR OF CHRONIC SCHIZOPHRENIC PATIENTS

FRED HEILIZER, PH.D.[1]

There are three questions that one may raise when evaluating the effects of a drug as a therapeutic device among psychiatric patients: 1) Does the drug work? Does it result in improvement in the general condition of the patients? 2) How does the drug work? What areas of behavior are affected? 3) Do the measures used reflect the process which is under investigation?

The measures used in this study were selected on the basis of the above questions. Reaction time and finger dexterity tests were selected because they seem to be especially sensitive to the schizophrenic process. The data presented in King's monograph (4) indicate that measures of fine motor movement yield clear distinctions among groups on the normal-neurotic-psychotic continuum. In addition, the distribution of scores for the schizophrenic group satisfies the expectation of extreme variability while the distribution for the normal group falls within a much narrower range. The Lorr Interview Scale was utilized to provide measures of change in relatively specific areas of behavior as well as a general morbidity measure. The Bender-Gestalt test was utilized to provide a measure of perceptual-motor performance.

METHODS

Sixty-four chronic schizophrenic male patients were randomly divided into a chlorpromazine group (300 mg/day) and a placebo[2] group for a period of three months. Each subject received medication from one of four bottles, labeled "A, B, C, or D." The pharmacist filled two of the bottles with chlorpromazine and two of the bottles with placebo according to a prearranged code. None of the patients had been lobotomized or were receiving tranquilizers. (Only six of the subjects had received tranquilizers at any time during their hospitalization. All six had received small dosages for short periods of time and no more recently than one year previous to the start of the study.) In general, the sample consisted of withdrawn patients who caused a minimum of difficulty to the hospital personnel. Forty-eight of the 64 subjects were successfully interviewed for the Lorr Scale (6) before medication and again 12 weeks after the start of medication. Forty-four subjects successfully completed the reaction time (4), finger dexterity (4), and Bender-Gestalt (2) tests before medication and again at two and eight weeks after the start of medication. The average age of these 44 subjects was 45.5 years and the average length of hospitalization was 14.2 years with standard deviations of 9.0 years and 7.0 years, respectively, and ranges of 26–69 years and 3–32 years, respectively. Half of the subjects completing each task were in the drug group and half were in the placebo group.

At the end of the three-month medication period, all subjects received placebo for six weeks and were then retested. Thirty-two subjects (13 former drug subjects and 19 former placebo subjects) completed the re-

[1] Veterans Administration Hospital, Northampton, Massachusetts. This study was conducted at the VA Hospital, Canandaigua, N.Y. My sincere thanks go to Dr. Karel Planansky for his continuing assistance and support, to Drs. Benjamin McNeal, Daniel Davis, Emory Cowen, and G. Richard Wendt for their interest and support, and to the nurses and attendants on wards 9 and 37 who willingly spent so much of their time in humoring the experimenter.

[2] Placebos were generously supplied by Smith, Kline, and French.

action time, finger dexterity, and Bender-Gestalt tests. Thirty-eight subjects (17 former drug subjects and 21 former placebo subjects) completed the interview procedure.

In the reaction time task the subject was instructed to press down on one of two telegraph keys until a buzzer sounded, when he was to move to his right as fast as possible and depress a second telegraph key. The emphasis was on a single movement, upon hearing the buzzer, from the key on the left to the key on the right. This procedure was repeated for a total of ten trials and produced two measures: lift and jump reaction time. The lift reaction time was the time it took the subject to lift his finger off the first telegraph key after the buzzer had sounded. The jump reaction time was the total time it took the subject to depress the second key minus the lift reaction time. Both measures were recorded in hundredths of a second and were computed as the average of ten trials. During the course of the testing the experimenter was struck by the marked variability of the subjects' reaction times within a block of ten trials. On the basis of this observation, variability scores were computed for the lift and jump reaction times, separately, by computing a standard deviation for each set of ten trials. A finger dexterity test was utilized which required the subject to place as many pegs as possible into a series of holes within 30 seconds. This task consisted of three trials on the Purdue Pegboard with the right hand, three trials with the left hand, and three trials with both hands at the same time. A single average score constituted the finger dexterity measure. The Bender-Gestalt is a widely used diagnostic and research tool which has been demonstrated to distinguish among diagnostic groups. It is a perceptual-motor task in which the subject is instructed to copy nine geometric designs as they are presented, singly, by the experimenter. The Bender was scored by the Pascal-Suttell (7) scoring system after satisfying the requirement of scorer reliability ($r = .94$) by scoring the records presented in their monograph. This scoring system provides a single score which is based upon a quantification of the "goodness" or, rather, lack of "goodness" of the drawings of the various designs. The Lorr Interview Scale was completed on the basis of interviews ranging from 20 to 50 minutes. This scale can be used to provide a total morbidity measure which is the sum of the absolute deviation from a norm for each of seven factors. (The factors are labeled: A—retarded depression vs. manic excitement; E—melancholy agitation; K—conceptual disorganization; F—perceptual distortion; G—motor disturbances; C—paranoid projection; J—self-depreciation vs. grandiose expansiveness.) The factors were also treated individually by computing the arithmetic deviation from a norm (the factor score for the subject minus the norm for the factor) for each factor. Four of the factors (K, F, G, C) are unipolar so that deviations from the norm can occur in only one direction, *i.e.*, scores which are arithmetically positive. Optimal behavior for these factors is represented by a score of zero and increasingly positive scores represent increasingly deviant behaviors. The three bipolar factors (A, E, J) also represent optimal behavior by a score of zero. Deviations for the bipolar factors, however, can be either positive or negative with increasingly positive scores and increasingly negative scores representing increasingly deviant behaviors in different (opposite) directions. Thus, for factor A, positive deviations represent manic excitement and negative deviations represent retarded depression; for factor E, positive deviations represent agitation and negative deviations represent depression; for factor J, positive deviations represent grandiose expansiveness and negative deviations represent self-depreciation. No attempt was made to secure additional raters to establish inter-rater reliabilities. However, the test-retest

TABLE 1

Means and Standard Deviations for the Drug Group and the Placebo Group

	Session		RT: Mean		RT: Variabil.		F.D.	Bender
			Lift	Jump	Lift	Jump		
Drug Group	Pre	Mean	33.4	68.5	10.0	19.7	34.5	71.6
		S.D.	20.1	88.6	8.0	27.3	7.3	45.1
	2 wks.	Mean	33.9	47.9	10.1	10.2	35.8	65.4
		S.D.	17.5	35.5	9.6	13.7	5.8	49.1
	8 wks.	Mean	28.4	45.1	8.9	8.0	36.6	64.6
		S.D.	11.8	25.2	7.2	5.6	5.8	47.7
Placebo Group	Pre	Mean	33.9	59.0	11.9	15.6	32.6	71.0
		S.D.	22.1	46.4	10.8	14.7	7.6	39.3
	2 wks.	Mean	42.3	64.0	15.5	15.6	35.3	67.7
		S.D.	30.2	61.7	17.7	16.0	8.3	35.7
	8 wks.	Mean	33.9	62.8	11.8	17.0	36.3	70.4
		S.D.	23.2	56.8	16.9	17.9	8.5	37.1

Lorr Interview Scale

	Session		A	E	K	F	G	C	J	Total
Drug Group	Pre	Mean	−1.00	0.62	6.21	3.54	2.12	2.12	−0.08	19.5
		S.D.	4.12	1.79	4.82	3.35	2.39	2.57	1.66	14.2
	12 wks.	Mean	−1.75	−0.08	3.46	2.58	2.46	0.71	−0.12	15.2
		S.D.	3.86	1.76	3.77	2.66	2.65	1.40	1.37	10.9
Placebo Group	Pre	Mean	−0.67	0.96	6.79	3.17	2.29	1.96	−0.21	20.4
		S.D.	3.72	2.44	4.45	2.78	2.34	2.49	1.74	12.1
	12 wks.	Mean	0.54	1.29	5.62	3.87	2.37	1.04	0.46	18.4
		S.D.	2.87	2.47	4.46	3.57	2.34	1.99	2.63	12.4

correlation of .77 on the total interview morbidity measure indicates adequate rater reliability. The experimenter administered and scored all of the above tests without knowledge of the subjects' medication.

In addition to the measures described above, weight measurements were taken on the same subjects as part of a parallel study, described more completely elsewhere (8). Some of the weight data are included in the correlational analysis (Table 4) for the purpose of emphasizing the generality of a particular relationship.

RESULTS[3]

The means and standard deviations of the 14 measures are presented in Table 1.

[3] All significance levels mentioned in the text are at the .05 level of probability, or less, according to a two-tail test. In the Tables, * = .05 probability level and ** = .01 probability level.

Analyses of variance computed for the premedication scores indicated no significant difference between the drug group and the placebo group on any of the 14 measures, either in terms of the total group or in terms of division into high, middle, and low initial scores (see below).

Our primary interest was to test for the differential effect of drug vs. placebo during the three months of medication. This effect was evaluated by the use of a mixed design, Type I, analysis of variance (5). The Type I analysis of variance provided for the evaluation of three sources of variance (experimental effects): medication, testing session, and the interaction between medication and session. We were not interested in the session effect since it reflected the differences among sessions regardless of medication. Similarly, we were not inter-

ested in the medication effect since it reflected the difference between the two medication groups regardless of sessions. Since the two medication groups were not significantly different during the first session (premedication scores) we had no reason to expect them to be different for the total of two or three sessions other than a drug vs. placebo difference which occurred during medication, *i.e.*, the difference between the means of the two medication groups was different on the one or two medication sessions as compared to what it was on the premedication session. This difference between the two medication groups on one session as compared to another session, *i.e.*, the drug effect, was reflected only by the interaction between medication and session.

Another interest was to determine the drug effect in relation to the subjects' status at the start of the study. This was done by dividing each of the medication groups into high, middle, and low on the basis of initial (premedication) scores for each measure, separately, and evaluating the data by the use of a mixed design, Type III, analysis of variance (5). The Type III analysis of variance provided for the evaluation of four additional experimental effects as well as the three experimental effects provided for in the Type I design: (a) the initial score effect; (b) the interaction between initial score and testing session; (c) the interaction between initial score and medication; and (d) the interaction between initial score, medication, and testing session. The interaction between initial score, medication, and testing session was the only one of these four effects which could reflect a drug effect which varied according to initial score grouping.

Thus, the drug effect for the total group was evaluated by the session x medication interaction in a Type I or a Type III analysis of variance. The drug effect in relation to initial scores was evaluated by the session x medication x initial score interaction in a Type III analysis of variance. The pertinent mean squares are presented in Table 2. The *F* ratios are not presented since they can be directly obtained from the ratio: interaction/error. The probability levels indicated in Table 2 refer to the *F* ratios so obtained.

An examination of Table 2 indicates that a significant drug effect was obtained for the total group on the variability jump reaction time and on the A factor (retarded depression vs. manic excitement) and the F factor (perceptual distortion) of the Lorr Interview Scale. An examination of Table 1 indicates the interpretations to be made of the three significant drug effects. The drug effect for the variability jump reaction time reflected a decreased variability for the drug group as compared to the placebo

TABLE 2

Pertinent Mean Squares of the Type I and Type III Analyses of Variance

Source	df	RT:Mean		RT:Variability		F.D.	Bender	df	Lorr Interview Scale							Total
		Lift	Jump	Lift	Jump				A	E	K	F	G	C	J	
Type I																
Sess × Med	2	176.06	2581.58	35.28	502.30*	7.88	109.93	1	23.01*	6.52	15.04	16.67	0.37	1.51	3.02	44.02
Error	84	143.63	1230.19	69.88	124.24	11.87	238.88	46	5.55	3.39	5.15	4.41	2.36	2.52	2.89	37.23
Type III																
Sess × Med	2	176.06	2581.58	35.28	502.30**	7.88	109.93	1	23.01*	6.52	15.04	16.67*	0.37	1.51	3.02	44.02
Sess × Med × Init Sc	4	111.30	643.13	36.33	326.79*	6.71	187.97	2	5.78	3.78	1.82	9.45	1.62	0.78	2.15	19.50
Error	76	132.77	1126.19	72.15	95.43	11.79	238.40	42	4.79	2.71	4.28	3.75	2.17	1.38	2.78	30.87

TABLE 3

Analyses of the Variability Jump Reaction Time for High, Middle, and Low Initial Score Groups

Initial Score Group		Means			Analyses of Variance		
		Pre	2 wks	8 wks	Source	df	M.S.
High	Drug	47.4	21.3	12.7	Sess. × Med.	2	1083.93*
	Placebo	33.0	27.6	33.3	Error	24	224.17
Middle	Drug	9.0	4.6	5.9	Sess. × Med.	2	68.08
	Placebo	10.4	14.2	11.2	Error	28	59.88
Low	Drug	4.1	5.6	5.6	Sess. × Med.	2	3.88
	Placebo	4.3	5.3	7.3	Error	24	8.16

group, since the drug group changed from 19.7 to 8.0 as compared to a change from 15.6 to 17.0 for the placebo group. The drug effect for the A factor of the Lorr Scale reflected an increased depression for the drug group as compared to the placebo group, since the drug group changed from −1.00 to −1.75 as compared to a change from −0.67 to +0.54 for the placebo group. The drug effect for the F factor of the Lorr Scale reflected a decreased perceptual distortion for the drug group as compared to the placebo group, since the drug changed from 3.54 to 2.58 as compared to a change from 3.17 to 3.87 for the placebo group.

Table 2 also indicates that a significant session × medication × initial score interaction was obtained on the variability jump reaction time. We can conclude that the drug effect, on this measure, was not the same for each of the three initial score groups. When each of the initial score groups was analyzed separately (Table 3), a significant drug effect was obtained only for the high initial score group. We can conclude that a significant drug effect was evidenced on the variability jump reaction time for the high initial score group, but not for the middle and low initial score groups. The drug effect for the high initial score group reflected a decreased variability for the drug group as compared to the placebo group, since the drug group changed from 47.4 to 12.7 as compared to a change from 33.0 to 33.3 for the placebo group.

TABLE 4

Intercorrelations of the Change Scores of Variables Yielding a Significant Drug Effect†

	Drug Group				Placebo Group			
	RT	Weight	A	F	RT	Weight	A	F
RT	—	−.46*	−.46*	−.25	—	−.03	.04	−.23
Weight	20	—	.70**	.06	20	—	.29	−.05
A	20	22	—	.00	19	25	—	.25
F	20	22	20	—	19	25	19	—

† The number of subjects are indicated in the lower left of each matrix.

Rank order correlations were computed among all the variables demonstrating a significant drug effect. (Included here are the weight measurements taken on the same subjects as part of a parallel study (8).) The correlations were computed separately for the two groups, utilizing change scores between the first and last session for each subject (Table 4). Analysis of the drug group indicates a series of significant intercorrelations among change scores of the variability jump reaction time, weight, and the A factor. The −.46 correlations between variability jump reaction time, on the one hand, and the weight variable and the A factor of the Lorr Scale, on the other hand, indicate that the drug subjects who became more consistent (less variable) on the reaction time test also tended to gain weight and become less depressed (A factor). The correlation of .70 between weight and the A factor indicates that the drug subjects who gained weight also tended to become less depressed. These three significant correlations indicate that the drug

subjects tended to change on these variables together, as part of a general matrix of change. Changes on the F factor of the Lorr Scale appear to be independent of changes on the other variables since it did not demonstrate any significant correlations. No significant correlations were obtained for the placebo group.

The final series of analyses were to involve the postmedication effect for the various significant variables. We had expected to find, at the end of the six-week postmedication trial, either a significant reversal of the drug effect (medication x session interaction) which had been previously observed, or a continuation of this drug effect (medication effect). The absence of either of these findings on any but the A factor indicates that the subjects who completed this section of the study were not typical of the subjects who completed the previous part of the study. The finding of a significant reversal of the drug effect on the A factor ($F = 5.78$, df $= 1/36$) must thus be interpreted with caution.

DISCUSSION

The analyses of variance of the previous section indicate that chlorpromazine, as compared to placebo, initiated a more consistent jump reaction time, an increased depression on the A factor of the Lorr Scale, and a decreased perceptual distortion on the F factor. The A factor, labeled retarded depression vs. manic excitement, consists of ratings of affect, mood swings, and level and amount of speech. The F factor, labeled perceptual distortion, consists of ratings of hallucinations, delusions, hostile impulses, and orientation for people. It is our feeling that the A factor, as applied to this sample (withdrawn chronic schizophrenic patients), is better labeled as an alertness factor and that the F factor indicates contact with the real world. The data, then, indicate that the drug group, as compared to the placebo group, became less alert and more oriented to the real world, as well as more consistent on a test of fine motor movement (variability jump reaction time).

The occurrence of these drug effects in the absence of a drug effect for the general morbidity measure (the total Lorr Interview Scale) indicates that chlorpromazine did not produce a general, indiscriminate, behavioral change but, rather, acted more or less selectively. Additionally, if it is assumed that consistency of response is "better" behavior than variability of response, then it appears that chlorpromazine initiated "better" behavior on two variables (variability jump reaction time and the F factor) but "worse" behavior on the third variable (the A factor).

The attempt to evaluate the drug effect in terms of the subjects' premedication behavior yielded inconclusive results. The variability jump reaction time analysis indicated that the subjects who were initially most variable demonstrated the greatest drug effect. However, there were no significant relationships between premedication behavior and the drug effect on either the A or the F factor of the Lorr Scale.

The rank order correlations indicated a general positive relationship among changes within the drug group on the variability jump reaction time, weight, and the A factor: subjects tended to do "better" or "worse" as part of a general matrix of change. There are two points of special interest here. First, the F factor, which encompasses hallucinatory and delusional behavior, was not part of the general matrix of change. This seems to be an important finding in view of the heavy emphasis placed upon this area of behavior by many investigations (3, 9). Although these results do not mitigate the importance of changes in these behaviors, they do indicate that these behaviors constitute a relatively isolated area of change (1). Secondly, there seem to be two discrepant drug effects as measured by the A factor. On the one hand, chlorpromazine reduced the level of alertness for the group as a whole (analysis of

variance) but, on the other hand, there was a positive relationship between increased alertness (and/or *less* decreased alertness) and more consistent jump reaction time and gain of weight (rank order correlations). Thus, despite the reduction in the level of alertness for the chlorpromazine group, those subjects within this group who became more alert, or who showed the least reduction of alertness, also tended to become more consistent on the variability jump reaction time and to gain weight. We would suggest, as a tentative hypothesis, that high dosages of chlorpromazine interfere with improvement of this matrix of behaviors and that the general procedure of increasing dosage levels, in the absence of marked behavior changes, may warrant more careful examination.

It is pertinent to indicate that none of the measures which were selected for this study on the basis of apparent sensitivity to the schizophrenic process (mean lift and jump reaction time and finger dexterity) yielded a significant drug effect. Despite the impressive changes for the drug group on the mean reaction time measures, and especially on mean jump reaction time (see Table 1), the variance of these measures was so great that the null hypothesis could not be rejected. Additionally, it might be noted that the premedication mean jump reaction time measure correlates .94 with the premedication variability jump reaction time measure, the latter measure yielding a significant drug effect. It might be profitable, in future drug investigations, to assume that the mean jump reaction time measure reflects the schizophrenic process but, because of the large variance, requires a large subject sample in order to adequately evaluate any true differences which might occur.

SUMMARY

Sixty-four chronic schizophrenic male subjects were randomly divided into a chlorpromazine group (300 mg/day) and a placebo group for a period of three months. Forty-eight subjects completed the interview for the Lorr Interview Scale before medication and again 12 weeks after the start of medication. Forty-four subjects completed the reaction time, finger dexterity, and Bender-Gestalt tests before medication and again at two and eight weeks after the start of medication.

Analyses of variance indicated that the drug group as compared to the placebo group, demonstrated a more consistent jump reaction time, a reduced level of alertness, and an increased contact with the real world. Attempts to relate the drug effect to premedication behavior were inconclusive. Rank order correlations for the drug group indicated that changes on the variability jump reaction time, weight, and the A factor of the Lorr Scale were part of a general matrix of change. Some implications of these data were briefly discussed.

A six-week follow-up investigation of withdrawal effects with 32 subjects indicated an increasing alertness for the former chlorpromazine subjects as compared to the former placebo subjects. However, this result was limited by an apparently atypical sampling subjects for the withdrawal study.

REFERENCES

1. Barsa, J. A. The dual action of tranquilizers. Am. J. Psychiat., **114**: 74–75, 1957.
2. Bender, Lauretta. A visual motor Gestalt test and its clinical use. Amer. Orthopsychiat. Assoc., Res. Monog. No. 3, 1938.
3. Himwich, H. E. Psychopharmacologic drugs. Science, **127**: 59–72, 1958.
4. King, H. E. *Psychomotor Aspects of Mental Disease*. Harvard Univer. Press, Cambridge, 1954.
5. Lindquist, E. F. *Design and Analysis of Experiments in Psychology and Education*. Houghton Mifflin Co., New York, 1953.
6. Lorr, M. Multidimensional scale for rating psychiatric patients, Hospital Form, Washington, D. C.: Veterans Administration T. B., 10–507, 1953.
7. Pascal, G. R. and Suttell, Barbara J. *The Bender-Gestalt Test*. Grune & Stratton, New York, 1951.
8. Planansky, K. and Heilizer, F. Weight changes in relation to the characteristics of patients on chlorpromazine. J. Clin. & Exp. Psychopathol., 1959. In press.
9. Truitt, E. B. Some pharmacologic correlations of the chemotherapy of mental disease. J. Nerv. & Ment. Dis., **126**: 184–210, 1958.

EARLY SEPARATION FROM THE MOTHER IN SCHIZOPHRENIA

MORTON BERG, M.D.[1] AND BERNARD B. COHEN, PH.D.

In the clinical experience of the authors, a recurrent theme found in the history of hospitalized schizophrenic patients has been that of permanent separation from the mother in early childhood. Early separation from the mother is felt to be a pathogenic experience. How disorganizing to personality development is such separation? Is it related significantly to schizophrenia? Or is maternal separation equally prevalent among the neuroses? This study is an inquiry into the relative frequency of permanent maternal separation in comparable schizophrenic and neurotic populations.

The relationship with the mother, as stated by Freud, forms the basis for all subsequent relationships with love objects. "Mother's importance is unique and without parallel, the strongest love object and prototype of all later love relations for both sexes (2)." Ego development finds its core in the relationship with the mother, according to Erikson. "Mechanisms of introjection and projection which prepare the basis for later identifications depend for their relative integration on the satisfactory mutuality between mothering adults and the mothered child. Only the experience of such mutuality provides a safe pole of self feeling from which the child can reach for the other pole: his first love objects (1)."

A number of studies have explored the relationship between separation from a parent and schizophrenia. However, these have not specifically dealt with permanent maternal separation during early childhood. In a case history of 50 male and female schizophrenics, Lidz and Lidz (3) found that by the age of 19, 40 per cent of the patients had lost a parent through death, separation, or divorce. The schizophrenic group was compared to two control groups, one consisting of psychotically depressed clinic patients and the other consisting of medical students; in the former, the frequency for separation from parents was 20 per cent, in the latter 17 per cent. However, it was stated that separation referred only to a parent, not specifically the mother; it was also pointed out that in the control groups parental separation was not necessarily permanent.

Wahl (6) studied the history of 392 male and female schizophrenic hospitalized patients, and found that 43 per cent lost one or both parents through death or separation before the age of 15. In comparing the incidence of parental death in his group of patients with the incidence in the general population, he observed that four times as many had lost a parent by death before the age of 15. No controls were employed in this study.

Unlike the above studies, the present research deals only with permanent physical separation from the mother, and particularly stresses such separation before the age of six years.

DELIMITATIONS AND DEFINITIONS OF TERMS

In the present investigation, only female subjects were employed, and only separation from the mother was investigated. "Separation," as used in this study refers to evidence of permanent separation from the mother before the age of six. "Mother" refers to the real mother and not to mother substitutes.

HYPOTHESIS

The hypothesis was that schizophrenic females will show a greater frequency of separation from the mother than will neurotic females.

[1] 5579 North Park Avenue, Philadelphia, Pennsylvania. The authors gratefully acknowledge the cooperation of Eugene L. Sielke, M.D., Superintendent, and his staff, Philadelphia State Hospital, and O. Spurgeon English, M.D., and his staff at the Temple University Psychiatric Clinic.

POPULATION

Age and Diagnosis. The experimental population consisted of two groups: 40 schizophrenic females at a state hospital, and 40 neurotic females who had been referred to the psychiatric clinic of a general hospital. In both groups, the subjects were between the ages of 20 and 40. Diagnosis in each case was made by the agreement of at least two psychiatrists. The types of schizophrenia and neurosis are indicated in Tables 1 and 2.

TABLE 1

Distribution of Patients According to Type of Schizophrenia

Chronic Undifferentiated	16
Paranoid	16
Catatonic	8
Hebephrenic	0
Total	40

TABLE 2

Distribution of Neurotic Patients

Emotionally Unstable Personality	5
Anxiety Reaction	8
Adult Situational Reaction	4
Depressive Reaction	5
Phobic Reaction	2
Passive-Aggressive Personality	6
Obsessive-Compulsive Reaction	2
Inadequate Personality	2
Compulsive Reaction	1
Psychophysiological Disorder	4
Compulsive Personality	1
Total	40

TABLE 3

Race and Evidence of Separation

	Evident	Not Evident
Hospital		
White	5	11
Non-White	9	15
Clinic		
White	1	22
Non-White	0	11

TABLE 4

A Comparison of White and Non-White Patients in Both Groups with Regard to Separation

	Evident	Not Evident
White	6	33
Non-White	9	26

Chi square = 1.61; P between .20–.30

Racial Factors. The hospital population consisted of 16 white, one Chinese and 23 Negro patients. The clinic population comprised 23 white and 11 Negro patients, plus six patients whose race had not been indicated in the records. It is apparent that there was a larger number of Negroes in the hospital population, a preponderance that is statistiscally significant.

However, when the white and non-white patients in both groups were compared regarding frequency of separation from the mother, no racial difference emerged. This is indicated in Tables 3 and 4.

Thus, the hospital and clinic groups were not comparable racially. But since there was no significant relationship between race and incidence of separation, the racial incomparability was excluded as a factor that could bias the results of the study.

Socio-economic Factors. The socio-economic comparability of the clinic and hospital groups was determined by comparing the parental occupations of patients in both groups, and categorizing these occupations according to the classification system described in the Minnesota Scale for Paternal Occupations (4). Information concerning parental occupation was present in 28 of the hospital records and 18 of the clinic records. The distribution of these occupations is presented in Table 5.

TABLE 5

A Comparison of Hospital and Clinic Groups with Regard to Class of Paternal Occupation

	Occupational Classes		
	I & II	III, IV & V	VI & VII
Hospital	1	13	14
Clinic	3	9	6

Chi square = 3.1; d.f. = 2; P between .20–.30

There is no significant difference between the parental occupations of the hospital and clinic groups. Thus, employing parental occupations as a measure of socio-economic status, the two groups can be considered comparable. However, this conclusion may be qualified somewhat by the fact that evidence indicating parental occupation was not available for all the cases in the study.

PROCEDURE

The social history of patients admitted to the hospital and to the clinic beginning on the first of January, 1955, was evaluated. Investigated were 40 consecutive social histories in each group meeting the criteria of age and diagnosis. The presence or absence of separation from the mother was noted for each patient.

To obtain the 40 social histories for each group, it was necessary to examine a large number of records. For the hospital group, not every record contained a social history. After an initial screening for patients meeting the criteria of age and diagnosis, 137 records had to be examined to obtain 40 with a social history. For the clinic group, 83 consecutive female records were screened for age and diagnosis to obtain the 40 records used. Social histories were available in all the clinic records.

The fact that social histories are not obtained for all hospital patients raises the question as to whether or not there could have been a relationship between separation and the absence or presence of a history. To determine whether such a relationship did exist, the hospital group was compared with a second group which lacked social histories. This second group consisted of consecutive records beginning with January, 1955, meeting the same criteria of age and diagnosis employed for the experimental group. In these records, the admission note, the psychiatric abstract, and other available information were examined to determine whether or not there was evidence of separation. The frequency of separation from the mother in the history and non-history groups is indicated in Table 6.

TABLE 6

Evidence of Separation in the History and Non-History Groups

	Evident	Not Evident
History	14	26
Non-History	10	30

Chi square = .061; P between .80–.90

There was no significant difference between the cases having and lacking a social history, with regard to frequency of separation. Thus, there appears to be no relationship between separation and the absence or presence of a history.

RESULTS

The incidence of separation from the mother in both neurotic and schizophrenic groups is indicated in Table 7.

In the schizophrenic group, 14 of the 40 patients (35 per cent) gave evidence of physical separation from the mother before the age of six. The types of separations are listed in Table 8.

In the neurotic group, two of the forty patients gave evidence of separation. One

TABLE 7

Incidence of Separation in the Schizophrenic and Neurotic Groups

	Separation Evident	No Separation Evident	Totals	% Separation Evident
Schizophrenic	14	26	40	35
Neurotic	2	38	40	5

Chi square = 9.30; significant at .01 level.

TABLE 8

Types of Separation Found in the Schizophrenic Subjects

Death of the mother	9
Hospitalization of mother in state hospital	1
Desertion by mother	1
Placement in foster home	2
Divorce	1
Total	14

patient, who was diagnosed as an adult situational reaction, was reared by her grandmother and never knew her parents. The second, diagnosed as a passive-aggressive personality, was adopted at the age of six months.

In comparing the frequency of separation in the two groups statistically (See Table 7), the significant difference between the two groups appears to confirm our hypothesis that schizophrenic females show a greater frequency of separation from the mother than do neurotic females.

DISCUSSION

In this study, early separation from the mother was singled out from the many possible traumata in the childhood of adult female schizophrenic and neurotic subjects. A significantly greater frequency of separation was found among the schizophrenic subjects.

It is true that only 35 per cent of the schizophrenic subjects gave evidence of permanent physical separation from the mother. Permanent physical separation, then, cannot be considered the sole factor in the development of schizophrenia. Other factors, psychological, constitutional and unknown, are apparently operating in the remainder.

While a consideration of all the possible causes of schizophrenia is beyond the scope of this study, it can be speculated that factors analogous to permanent physical separation from the mother may have been operating in the remaining 65 per cent. For example, temporary separation may have had an effect comparable to permanent separation in a number of cases. Further, a maternal attitude of rejection may have had a psychological impact similar to loss of the mother.

While no direct causal relationship is established between maternal separation and schizophrenia, the results of this study support the point of view that the schizophrenic reaction originates in a pathological mother-child relationship. Rosen (5) feels that it is the rejecting or "perverse" mother who fixates the child at a psychotic level of adaptation. Our study would tend to support his view, for certainly there can be no more rejecting a mother than the departed one.

Why would schizophrenia be the choice of illness in response to separation from the mother? In discussing possible answers to this question, two areas that can be explored are the frustration of basic needs for gratification, and ego development.

The child is dependent upon the mother for the gratification of its earliest needs. Through the loss of the mother, the child would of necessity be exposed to intense tension stemming from unrelieved instinctual needs. The state of prolonged painful frustration may be a differentiating factor in the psychogenesis of schizophrenia and neurosis in our subjects.

In regard to subsequent personality development it can be speculated that schizophrenia as a symptom complex is a compromise between a vigorous seeking for, and avoidance of, the mother. Both of these extremes are in response to the overwhelming frustration of earliest needs. On the one hand, there are explosively aggressive attempts to obtain gratification from the mother or her substitute; on the other hand the painfulness of prior frustration initiates a defensive avoidance. It might be speculated that the dissociated speech of the schizophrenic is a manifestation of this extreme ambivalence; the meaninglessness on one level and meaningfulness on another represents symptomatically in speech the conflicting desire for avoidance and contact.

In the sphere of ego development, separation from the mother must exert a profound influence. The ego is the psychic representative of the external environment; it is the incorporation of past experiences with objects on the basis of which future action takes place. The first and most important object experience for all subsequent development is the mother. Arising out of the mother-child relationship is the sense of self relating to an outside world, which is repre-

sented at first by the mother. Erikson (1) suggests this experience is requisite for a normally developing ego. If the mother is lost the ego cannot evolve from a healthy core. A vacuum at the center of things is experienced; there is no sense of self on the one hand, and a perception of loneliness and isolation from the world on the other. This corresponds clinically with the schizophrenic's feeling of detachment and loss of identity.

From the foregoing, certain therapeutic implications arise. Some of the major goals in the treatment of schizophrenia would seem to be: 1) breaking through into the pathological vacuum created by the infantile loss of the mother, 2) recreating the mother-infant relationship in which the infant is gratified, 3) rebuilding the ego by supplying a good mother figure with which to identify, and finally, 4) in treatment, replacing painful frustration in human relationships with the experience of pleasure. Through this corrective experience the schizophrenic is supplied with what he missed as a child: a sense of self interacting with other humans for gratification.

SUMMARY

This study investigated the frequency of permanent physical separation from the mother in the childhood of hospitalized female schizophrenics. It was hypothesized that schizophrenic females would show a greater frequency of such separation than would neurotic females. Of the 40 schizophrenic subjects, 14 gave evidence of separation; of the 40 neurotic subjects, two only were found to have been separated. These results confirm the hypothesis, the difference between both groups being significant beyond the one per cent level of confidence.

In discussing the results of the investigation, the following areas were explored: 1) the significance of deprivation in the development of schizophrenia, 2) the relationship between separation and ego development, and 3) implications for psychotherapy with schizophrenic patients.

REFERENCES

1. Erikson, E. The problem of ego identity. J. Am. Psychoanal. A., **4**: 56–121, 1956.
2. Freud, S. *Outline of Psychoanalysis*. W. W. Norton, New York, 1949.
3. Lidz, R. W. and Lidz, T. The family environment of schizophrenic patients. Am. J. Psychiat., **106**: 332–345, 1949.
4. Univ. of Minnesota, Institute of Child Welfare. *The Minnesota Scale of Paternal Occupations*. Univ. of Minnesota Press, Minneapolis.
5. Rosen, J. *Direct Analysis*. Grune & Stratton, New York, 1953.
6. Wahl, C. W. Some antecedent factors in the family histories of 392 schizophrenics. Am. J. Psychiat., **110**: 668–676, 1954.

CHISHOLM, BROCK. *Prescription for Survival.* Columbia University Press, New York, 1957. 92 pp. $2.50

The most pressing question of our time is whether *homo sapiens* is to join the long line of species which became extinct because they could not adjust promptly enough to environmental change. By harnessing nuclear energy, mankind has so altered its environment that it cannot survive unless it drastically modifies some of its traditional behavioral patterns. It will require the utmost efforts of intellectual and political leaders to bring the necessary modifications about, if, indeed, they can be achieved at all.

In this book of less than one hundred pages, one of our foremost psychiatrist-statesmen offers a trenchant analysis of the present human predicament and makes a significant contribution towards its solution. As a former Director General of the World Health Organization, Dr. Chisholm speaks out of first-hand knowledge of the dangers created by mankind's new-found capacity to destroy itself, by overpopulation, and by the grotesquely unequal distribution of the world's wealth. He paints a vivid picture of the wretched state of most of the world's population and of their attitudes to the fortunate few who are oversupplied with goods and food. He explains the functions and severe limitations of the United Nations as a way of coping with these problems.

As a psychiatrist, Dr. Chisholm convincingly describes the crippling effects on mental development of punitive, authoritarian child-rearing practices which demand unquestioning acceptance of dogmas and inculcate a sense of sin. He shows how human survival in a rapidly changing, shrinking world requires that all of us develop "a freedom of attitude, an ability to recognize different circumstances, an ability to respect the sacredness of other people." (p. 59) and he describes the role of the imagination as a safety-valve for destructive impulses and a means of exploring reality, in pursuit of these ends.

His prescription for survival is essentially a plea for a type of upbringing which encourages the child to explore the world for himself and find his own solutions, instead of forcing him into the straitjacket of traditional attitudes, thereby perpetuating in each new generation the errors of the previous one.

The virtues of permissive non-dogmatic child-rearing are obvious to a Western psychiatrist, but one cannot help wondering whether they are equally apparent to most of the rest of the world. Everyone needs to develop a philosophy of life which, at some point, must rest on faith, since the human intellect is too limited to penetrate the mysteries of existence. Most humans need illusory certainties to help them overcome the anxieties of life, and the need is greater, the more menacing the conditions of life are. Perhaps the goal should be not to dispense entirely with the inculcation of dogmas, but to try to instill in the young those which are compatible with human survival rather than inimical to it.

The two attitudes which create the most immediate danger today are ethnocentrism and the assumption that war is normal. The immediate task is to replace these attitudes with loyalty to humanity and the recognition that war has become obsolete, which requires acceptance of the principle of non-violent settlement of disputes among nations. Dr. Chisholm's prescription might eventually bring these changes about, but whether that much time will be allowed is problematical.

If Dr. Chisholm has not produced an entirely satisfactory solution to the terrible dilemmas of our time, neither has anyone

else. The best hope lies in each person's making whatever contribution he can from his own point of vantage, as a stimulus to the thoughts of others. Dr. Chisholm's contribution is an impressive one, based on an unusual, if not unique, body of experience. It deserves to be widely read and pondered.

Jerome D. Frank

ALLAN, W. SCOTT. *Rehabilitation: A Community Challenge.* John Wiley & Sons, Inc., New York, 1958. 247 pp. $5.75

One significant aspect of medicine during the period since World War II has been the rapid development of rehabilitation centers. Such centers range from large programs in university settings for both out-patients and in-patients; using the disciplines of the various medical specialties, physical therapy, occupational therapy, social work, speech and hearing therapy, psychological services, recreation services, prosthetic services and rehabilitation counseling; to small out-patient programs providing physical therapy on the prescription of the referring physician. As compared to but a handful of such centers prior to World War II, there are nearly two hundred such centers in the United States today.

The author of this book has been closely identified with these developments as supervisor of medical services of the Liberty Mutual Insurance Company, one of the nation's largest carriers of casualty and workmen's compensation insurance. For many years he was the director of the rehabilitation center in Boston operated by the Liberty Mutual Insurance Company.

As a result of this experience, Mr. Allan has written a book which combines well-grounded theories and practical experience. The book gives practical and sound advice on the organization and operation of rehabilitation centers and includes discussion of such factors as capital budgets, operating costs and staffing patterns.

It also accurately reflects its title for it approaches the problem of rehabilitation from the community planning perspective. Although this book deals primarily with rehabilitation centers, there are chapters devoted to rehabilitation in the hospital, sheltered workshops and services for the homebound.

There has long been a need for a book devoted to community planning for rehabilitation and the organization and administrative aspects of rehabilitation. Mr. Allan has filled this need extremely well. This is a book which should be of value for all persons concerned with rehabilitation services for the handicapped.

Howard A. Rusk

EDWARDS, ALLEN L. *The Social Desirability Variable in Personality Assessment and Research.* Dryden Press, New York, 1957. viii + 108 pp. $2.75

It has long been recognized that scores on personality tests that require the subject to furnish a self-description may be distorted by a tendency—conscious or unconscious—to respond to the items on such tests in terms of the personally acceptable or the socially desirable. From this recognition, a considerable literature has developed on the subject of "faking" on personality inventories, but as Allen L. Edwards points out in his monograph, the results of studies in this area have shed relatively little light on the basic problems of measuring and controlling social desirability in personality assessment and research.

Edwards tells us that his interest in these problems arose some years ago, quite by accident, when he set out to investigate the interrelationships between various measures of attitudes and personality traits. He had not intended to develop new measuring instruments, but the paucity of personality inventories that dealt with the "normal" personality variables with which he was concerned led him to feel that a new inventory was required. It was at this point that

he found it necessary to face the problem of social desirability in personality testing, and to see what could be done about it.

His first approach to this problem made use of a group of judges to rate personality statements (test items) in terms of whether they considered them desirable or undesirable in others. The judges' ratings were then scaled to locate each statement on the continuum of social desirability. It was established that such variables as the age, sex, and socio-economic status of the judges did not materially affect the social desirability scale values of the statements investigated. An early study revealed a correlation of almost 0.90 between the social desirability scale value of a statement and the probability that the statement would be endorsed by a group of subjects when they were asked to describe their own personalities in terms of it. Later studies have yielded correlations of comparable magnitude for a rather wide variety of statements.

More recent work on social desirability has made use of a Social Desirability scale, composed of Minnesota Multiphasic Personality Inventory (MMPI) items which are heterogeneous in content and unequivocal as to social desirability or undesirability. Edwards reports sizable correlations between the Social Desirability scale and various personality inventories in common use. As predicted, these correlations are positive when a high score on the inventory corresponds to a socially desirable characteristic, *e.g.* cooperativeness or responsibility, and they are negative when a high score indicates a socially undesirable trait, *e.g.* introversion or hostility. Correlations between the Social Desirability scale and the clinical scales of the MMPI are consistently negative and of considerable magnitude, while the correlation between the Social Desirability Scale and the K scale of the MMPI, an index of "defensiveness" in taking the test, is positive.

To summarize the evidence, a substantial portion of the variance in scores on commonly employed personality inventories (and also in the Q-sorts which have come into wide use in the past few years) can be explained in terms of differences in the social desirability scale values of the items of which they are composed. The interpretation of performance on these inventories is thus complicated, for if an item has a high social desirability scale value and if a subject endorses it as descriptive of his personality, we do not know whether the item does, in fact, accurately describe his personality, or whether he simply says it does because he sees it as representing a socially desirable characteristic. Obviously a similar difficulty of interpretation arises when the subject fails to endorse an item with a low social desirability scale value. How, then, to control social desirability in personality inventories?

Edwards cites three approaches that have been suggested: the development of instruments composed entirely or primarily of items that are neutral in social desirability; the use of instruments such as his Social Desirability scale to correct scores on inventories for social desirability; and a third approach which he has employed in constructing the Edwards Personal Preference Schedule. In this inventory, statements are paired on the basis of their social desirability scale values as previously determined, and the subject is required to select the statement in each pair that is the more descriptive of his personality. This is known as the forced-choice approach. If the statements could be perfectly paired, it would clearly be impossible for the subject to choose between them on the basis of social desirability. With the excellent pairing achieved by Edwards on the Personal Preference Schedule, differences in social desirability scale values account for only about 15 per cent of the variance in the probability of endorsement of a statement, whereas when the same items are administered in the form of the conventional "Yes-No" type of inventory, differences in social desirabil-

ity scale values account for approximately three-quarters of the variance in the probability of endorsement. Edwards modestly claims "a fair degree of control over the tendency to give socially desirable responses" in his personality inventory.

The present monograph on social desirability is more than a summary of past research by Edwards and other investigators, and it is clear that the author does not regard the Personal Preference Schedule as the single final answer to the problem of controlling social desirability in personality inventories. He raises a number of provocative questions, and offers many leads for future research on this problem. We may anticipate that investigators will not be slow in following them up. (This reviewer would particularly like to see serious attempts made to control social desirability by means other than the forced-choice approach. The alternative approaches present many problems of their own, but may ultimately prove even more effective than forced-choice.) Edwards' monograph is not only stimulating; it is simply and clearly written and requires a minimum of statistical sophistication on the part of the reader. It is a must for those concerned with the construction of personality inventories, and all who use such tests either in research or in applied fields will profit from reading it.

A. B. Silverstein

SPRINGER, GEORG F., ED. *Polysaccharides in Biology*. Transactions of the Second Conference. The Josiah Macy, Jr. Foundation, New York, 1956. 245 pp. $5.00

The program of the Macy Foundation is so well known and has been so rewarding to investigators in almost any area of biology that a review of this conference is in many ways almost unnecessary. That the problem being discussed is timely and important is usual for the able planners of these meetings, as are their almost unique qualities of stimulation to the investigator and more than reasonably successful attempt to effect communication across the barriers of special training, language and bias.

The discussion in the present volume is centered about three presentations: 1) Sialic acid and related compounds, by F. Zilliken; 2) Interaction of Polysaccharides and Viruses, by F. L. Horsfall; and 3) Pyrogens, by O. Westphal. There is no need here to go into the microbiological and medical significance of these problems. What is more necessary, perhaps, is to point out the general interest of the discussion to investigators in many fields including those primarily concerned with nervous system problems. The basic broad area involved relates to the chemical nature and structure of certain substances with biological activity. Narrowed down even further (and of extreme significance to anyone with a bias in the direction of the importance of cell membranes in the responses of the organism) this becomes, in part at least, the problem of the chemical nature of inhibitors and of receptors on the cell surface which interact with particular molecules. In the present volume this specifically deals with, for example, the interaction of erythrocyte and virus, but interesting extrapolations can be made from this baseline.

In general, then, it suffices to say that the Macy Foundation has presented us again with a provocative and stimulating discussion of undeniable interest to students in many fields of biology and medicine.

Robert G. Grenell

SAKEL, MANFRED. *Schizophrenia*. Philosophical Library, New York, 1958. vii + 334 pp. $5.00

In beginning these comments it may be useful to say something about what is signified by a "review" of the work of someone other than one's self. Such a commentary may take several forms as suggested by the following: 1) A book (for example) is de-

scribed in such a way that the attention of those concerned with its study is drawn to it; 2) the subject matter is outlined, its "essence" being presented so effectively that hurried students may forego a detailed reading of the original; 3) the material is examined critically in an effort to make an objective presentation of its defects and excellences; or 4) an essay is written on the same general subject, the original presentation being expanded or developed from some particular point of view.

My remarks on the book entitled *Schizophrenia* by Dr. Manfred Sakel are probably best suited to the third category, and are better understood if I speak first of myself. Objectivity being an elusive ideal, I think it is important that something of the viewpoint of a reviewer be known, and that his observations be considered as relativistic (in terms of his bias, experience, interests) and not presented by him as absolute (that is, as necessarily the "right" or "only" way to look at things).

Some years ago, as student and resident physician, I met a goodly number of patients who bore the diagnosis Dementia Praecox or Schizophrenia. I talked with these people and certain of their relatives, I made diagnoses, and I arranged for "disposition"—usually a transfer of the patient from university clinic to state hospital. I often felt rejected by the patients, frequently seemed to make no sense in talking with them, and felt discouraged and inept as a physician. Much of what I had learned in school was not clearly relevant to my task with these patients, and I felt most at ease when I was "taking a routine history," making a physical examination, or carrying out the various laboratory tests with which I was familiar. With the completion of all these, and the discovery that the accumulated data often threw no great light on disorder, I was alone with the patient and my feeling of discomfort. I found it difficult to sit, to listen, to observe; I felt that I should be active and "doing something" to forward recovery from a state which I did not comprehend. This entire procedure was tinged with a sense of hopelessness and I tended to withdraw from the patients who seemed to me to be incomprehensible and beyond relief.

The introduction of insulin therapy brought some increase of hopefulness to me. Although the "cause" of schizophrenia was not made clear by the treatment, the procedures used were somewhat in accord with medical practices, there was a great deal of work to be done in making tests and caring for patients, and I had a sense of justifying my presence on the ward. The morale of the unit was improved and I felt more closely related to nurses, patients, and fellow physicians, drawn together in a common effort that seemed in keeping with the medical business of the rest of the general hospital.

With the passage of time I saw some patients grow better, some relapse, and others develop the complications of deep coma; I used metrazol (with dislike and early disapproval) and later was involved in the use of electroshock. There came a time—belatedly I think—when I once again turned my attention to my patient as a person (not as someone diseased and thus psychotic and estranged), to the social scene from which he had come and in which he lived, and to his relationship with me and my associates. As I listened I heard more, and I came to think that my patient's behavior was comprehensible in terms of my own living and was a reflection of his life experiences; I could no longer "believe" that schizophrenia was a disease of the brain in any ordinary sense of the word—or, for that matter, of a portion of the personality structure known as the ego. I turned my attention to intensive psychotherapy with schizophrenic patients (among others), and the word *interpersonal* became more meaningful to me as I discovered through extended courses of treatment that knowledge of my patient and of myself increased together. Although I could find that I had no special gift for

therapy I noticed that the "hopeless" frequently improved, that recovery was a matter of freeing natural processes of growth, and that illness and sickness were often subtle reflections of life experience and not irreconcilable differences to be explained by the presence or absence of diseased tissue. My comments on Dr. Sakel's book should be evaluated in terms of this experience of mine and of my continuing interest in intensive, and often prolonged, psychotherapy.

The book is divided into two parts. In Part I, "Etiology, Symptomatology and Psychopathology," there are ten chapters devoted to the consideration of such topics as "Man and His Mind," "Classification," "Etiology," "General Psychopathology," "Prognosis," "Paranoia," and so on. In Part II, "The Sakel Insulin Shock Treatment," the technique of the method is outlined in considerable detail.

In the first portion of the book the author attempts to distinguish between disorders of a psychological nature, and those belonging "to the realm of experimental physical medicine" and in which "a 'break' in the phylogenetically ingrained patterns and pathways of nervous responses which normally flow in an enforced course is the outcome of a noxa" (p. 26). Referring to the first group it is said that in speaking of cures psychiatrists "forget to take into consideration the fact that they were curing patients who were not really sick but superficially emotionally disturbed people who at most needed moral support and perhaps only flattery and self-justification" (p. 17). Schizophrenia is a term herewith applied to patients who have suffered structural "reversable damage in the biochemico-ionic or possibly electro-magnetic constellations of the invisible particles in the nerve cells" (p. 27).

The problem of etiology is considered at a number of points as exemplified by the following quotations. "Because of the proven effectiveness of the physiological approach to the disease schizophrenia, it can be assumed that the schizophrenic disease process is based entirely upon a physiological and communicative electrono-ionic disturbance, even though we are not capable of proving it by visible clinical or electrical tests" (p. 34). "... it is possible to assume that the diencephalon where we find the main centers of the vegetative nervous system is the primary seat of the schizophrenic disease process" (p. 34). "... it seems to be indisputable that the predisposition to have a weaker structure of the nervous system which results in its being overcome even by the normal life processes or prematurely exhausted is inheritable" (p. 43). "... Schizophrenia is a disease process in the nerve cell" (p. 49).... "Observation of the therapeutic effect of the individual factors of the Sakel Shock Treatment left little room for doubt that the basic cause of major psychoses, particularly schizophrenia, was predominantly pathophysiological in nature and not psychological" (p. 238).... "It is evident that heredity plays an important part in the development of this disease since about 50–60 per cent of the cases have a family record of mental illness" (p. 132). Ideas that schizophrenia is not a disease "are utterly erroneous, being based on a false premise, in not conceiving the schizophrenic disease process as physiological, biochemical and electrical malfunction" (p. 147).

I am inclined to view the schizophrenic process as a reaction to life experiences in which anxiety is a significant factor in the elaboration of behavior. I do not know what roles may be played by alterations in cellular structure, biochemical deficiencies, hereditary disorder, and so on; nor am I qualified to evaluate adequately studies of such phenomena. Colleagues in related fields of science have told me that the evidence for a basic structural or physiological defect in the schizophrenic reaction is at this time imperfect. In my opinion Dr. Sakel speaks too emphatically of alterations in nerve cells, and weakens his arguments by fre-

quent use of such phrases as "it is undeniable," it "can be definitely accepted," "we have to assume," and so on in discussing propositions that are of interest, but by no means undeniable or to be readily assumed.

The chapters on classification and etiology are brief and do not add to what has already been written on the subject, but are useful in that in them Dr. Sakel's point of view is presented. The section on examination describes an interview technique which may be suitable in assessing a patient's difficulties preliminary to the administration of insulin, but is not adequate as a guide to the interviewing of schizophrenic patients or of anxious people in general. In the chapter on symptomatology there is a discussion of schizophrenic behavior largely in terms of it being a reflection of organic disorder, as indicated by the following quotations. "The general belief that a delusion could possibly have anything to do per se with the individual's education or prevailing surroundings seems obviously to have no foundation in fact. It is a symptom of a disorder in the mechanism of the thought producing organ—the brain. The delusion must be considered solely as a symptom therefore of a disease which has befallen the organ which is responsible for distilling thought ..." (p. 82). "... depersonalization seems to be a mechanism produced by a disturbance in a particular organic center" (p. 87). "There seems to be no longer any doubt that my conceptions offered of the derailment and faulty isolation of the otherwise strictly isolated sensory intercellular pathways being responsible for hallucinations are valid." ... A hallucination, therefore, "cannot under any circumstances be explained by any psychological condition" (p. 88). The chapter on psychopathology is, in my opinion, fragmentary, poorly organized, and does not present any adequate statement of personality development or symptom formation.

In Chapter Seven, "Schizophrenia," Adolf Meyer's concept of the disorder is dealt with as follows: "It seems that Meyer's view that schizophrenia is not a disease but the outcome of progressive maladaptation of the individual to his environment can be considered redundant for the purposes of this book.... The success of experimental medicine in influencing the schizophrenic disease process, in temporarily arresting its course or in some cases bringing about a complete remission, seems to lend no support at all to Meyer's concept outlined above. One might even say that it eliminates a clinical-psychological or, as Meyer would say, a biopsychological approach to this disease, as not justified" (p. 135).

In a later section psychoanalytic observations are quickly dismissed: "The psychoanalytical explanation of schizophrenia seems, in view of the now established facts, to have no validity. The malignancy which the psychoanalysts try to deduce from symptomatology is simply an expression of a deep-seated physiological malfunction" (p. 162). There is no evidence in this volume that the author had any intimate knowledge of psychotherapeutic intervention in the schizophrenic process, and he includes no references to such workers in the field as Federn, Fromm-Reichmann, Kempf, Sullivan and Zilboorg, although Bleuler and Kraepelin are frequently mentioned.

In the book's second division the author describes the Sakel Insulin Shock Treatment, presenting (in Chapter Fifteen) a "working hypothesis" in an effort to explain the insulin effect. In the conclusion Dr. Sakel states the aim of the treatment as "a physiological 'destruction' of the irreparably diseased cells, and the forcing of the dormant and healthy cells to take over the specific functions and normal activity in their place.... The cure is affected in this treatment not by convulsions but primarily by treading a very narrow safety line of a very prolonged coma, which starves out the diseased cells and permits the dormant ones to come into action in their stead" (p. 334).

If this book is, in accordance with its title, to be looked upon as a discussion of the schizophrenic process, it is, I think, inadequate. There is no developed presentation of personality theory, of the role of anxiety in human behavior, of psychotherapy, of ward management, or of nursing care. In view of the numerous references to structural and physiological changes in the nervous system there is very little presented as supporting evidence in the form of studies in biochemistry, neurophysiology, and pathology.

The section on the use of insulin is of particular interest to me because of the extensive work done by Dr. Sakel with this form of therapy. However, this portion of the book does not include a report of follow-up studies, statistics regarding the therapy as used by the author or other psychiatrists, reports of brain damage and fatalities, details of nursing care, or a record of psychological studies (such as the use of projective techniques). Some references are made to post-convulsive brain damage but few data are provided. In speaking of his use of insulin therapy Dr. Sakel does himself an injustice in not including certain information gained by other workers in this field.

The material in this volume is loosely organized and often repetitive, being in need of further editing, which could be usefully provided in any later editions. There is a brief index of author's names, but their writings are not mentioned by title, and quotations in the text are usually given without the source being named. The lack of a subject index and bibliography markedly reduces the usefulness of the book as a reference.

Although I find much to criticize in this book I am glad to be able to read Dr. Sakel's exposition of his concept of schizophrenia and his use of insulin therapy. I am also impressed by Dr. Sakel's obvious great concern with the psychiatrist's failure to comprehend or cure much of that which he is required to treat. He says, "The history of psychiatry abounds with theories, postulations, dogmatisms and persuasive treatments which are only rivaled in "quantity by the lamentable lack of cures" (p. 7). I gather that he was driven in part by his knowledge of "the misery which still exists in the overfilled mental hospitals," where patients remain "unhelped in the gravest of human diseases, sometimes spending their entire lives incarcerated as has been the case for centuries" (p. 7).

It seems to me that a more appropriate title for this volume might be *The Theory and Technique of Insulin Therapy as Applied to Schizophrenia*, and as such might be looked upon as the expression of the thinking of a dedicated and experienced psychiatrist who would not accept a concept of schizophrenia as an irreversible process, and labored to advance our knowledge of the disorder and to bestir the medical profession to taking a further interest in the schizophrenic reaction, and, perhaps, slowly becoming more hopeful about its outcome.

We physicians see the disorders with which we deal from varied points of view, our concepts being dependent upon our training, our life experiences, the cultures in which we live, the situations in which we treat our patients, and our personalities which contain the bias whereby perception is distorted in the service of necessity and self-esteem. Often we may not agree upon our observations or the conclusions drawn from them, but we are bound to state what we have seen and what we think as clearly as we can, trusting that thus truth may become more evident. It is not required that we convince each other; it is enough that we may learn at times from our exchanges. Relevant to this comment is a passage from the book *The Plague* by Albert Camus (p. 197, Alfred A. Knopf, New York).

At the height of the plague the priest says regretfully to the doctor, "And yet—I haven't convinced you!"

Replied the physician, "What does it matter? What I hate is death and disease, as you well know. And whether you wish it or not, we're allies, facing them and fighting them together."

Otto A. Will, Jr.

BROADBENT, D. E. *Perception and Communication.* Pergamon Press, New York, 1958. 338 pp. $8.50

It is exciting to watch someone synthesize meaningful patterns out of apparently incoherent observations. This book would be worth reading just for the pleasure of following Broadbent through the maze of observations to his final propositions. Add to this a brilliant insight into the vexing problems of attention and the result is a really major contribution to the study of human behavior.

The human nervous system has limits. Sensory data is dealt with in sequential patterns. If instantaneously available sensory data did not exceed the input capacity of the central nervous system (which it often does), then the almost infinite sequential possibilities would certainly pass this "channel capacity" limit. To deal with this state of affairs, the central nervous system must resort to filtering, coding, and short-term memory. Loads that sense data impose on the nervous system are related to information content. For example, two physically identical stimuli can produce quite different loading if they are drawn from different ensembles of possibilities. When the input exceeds capacity, then filtering can exclude non-pertinent stimuli and altered coding can reduce the load imposed by stimuli that the filter passes. Data rejected by the filter can be stored for a short while in a "short term memory" and recovered for a few seconds but will decay and vanish if not utilized within that limit.

A brief review cannot do justice to the details contained in the book. Many characteristics of the filter and the short term memory are discussed in detail; various coding systems are dealt with; vigilance, skill, learning, conditioning and extinction are well considered in relationship to this model; and a final overview is presented in the last chapter. Controversial interpretations are given to some observations but each interpretation is unambiguous and testable. Furthermore, the general model suggests a host of other questions to be posed in experimental design.

The book is written from the viewpoint of human engineering and so might be overlooked by those who use other approaches to the study of behavior. This would be most unfortunate. Clinicians have long recognized that the selective nature of attention is a crucial factor in many psychological defense mechanisms. Current neurophysiological work on the ascending reticular system is furnishing physiological insights into how attention may be mediated. Psychopharmacologists work with drugs that influence alertness and attention. Unfortunately, in each of these fields, the use of everyday language causes confusion. Words like "perception," "sensation," "attention" and "cognition," are too vague for scientific communication and theories phrased in these terms lead to ambiguous predictions. Broadbent uses a modified communication engineer's vocabulary but his definitions are aptly fitted to the needs of the behavioral scientist. As a result, the model he proposes should help clarify thinking in clinical psychiatry, neurophysiology and psychopharmacology, as well as in human engineering and experimental psychology.

In summary, this book is a "must" for anyone seriously interested in the "hows" and "whys" of getting data into the human central nervous system.

Enoch Callaway, III

SCOTT, JOHN PAUL. *Aggression.* The University of Chicago Press, Chicago, 1958. xi + 149 pp., illus. $3.75

This book presents an admirable analysis of a fundamental problem. Aggression is defined as follows: "... 'aggression' refers to fighting and means the act of initiating an attack." The author examines the problem from many points of view. He discusses the contributions of Pavlovian psychology, psychoanalysis, social psychology, cultural anthropology, neurophysiology and experimental psychology, and draws upon a wealth of experimental studies and observations on many species of animals. Although he does not go deeply into all of the areas which are covered, the author shows considerable familiarity with his subject matter. Many of the studies reported were done by the author himself. As the book progresses the reader is introduced to the subject of aggression, beginning with its more elementary aspects and finally arriving at its most complicated expressions in the form of group conflicts and human warfare. The major points which the author makes are as follows. (a) "... aggression, in the strict sense of an unprovoked attack, has to be learned," and one can also learn *not* to fight. (b) We can also conclude that there is no such thing as a simple "instinct for fighting," in the sense of an internal driving force which has to be satisfied. "There is, however, an internal physiological mechanism which has only to be stimulated to produce fighting.... The internal physiological mechanism is dangerous, but it can be kept under control by external means." (c) "... there is no need for fighting, either aggressive or defensive, apart from what happens in the external environment. We may conclude that a person who is fortunate enough to exist in an environment which is without stimulation to fight will not suffer physiological or nervous damage because he never fights." (d) It is not desirable to control aggression entirely by "inhibitory" means, but it is well to allow some outlets.

The author, a zoologist by profession, is well aware of the human psychological problems of aggression. He gives them ample consideration and discusses the harmful consequences to the individual when aggression is suppressed (although he does not give adequate consideration to the problem of *repression* as opposed to suppression). He also avoids the mistake of regarding aggression in its pure or sublimated forms as an unmitigated evil. Consideration is given to its constructive aspects.

Finally, in discussing the problem of warfare Dr. Scott looks for no simple explanation or solution to this extremely complex social phenomenon but suggests that further scientific study may contribute to solution of this greatest of all social problems.

The prospective reader may wonder whether the author is overambitious or over-optimistic in attempting to bring together such traditional "rivals" as psychoanalysis and Pavlovian psychology; but it is here that Dr. Scott shows great skill and understanding. He is able to extract from each field whatever concepts are most useful for understanding the problem. As a result he finds harmony rather than conflict.

One may also be inclined to ask whether animal studies can offer anything to the understanding of human psychology, which is so much more complex. But after reading this book only the most skeptical readers will fail to be impressed with the weight of evidence presented by the author. In its relative simplicity, the data from the animal studies described points up general biological trends which tend to be obscured by the complexities of human psychology. Although Dr. Scott is generally careful in making his inferences, he does take for granted that man fits in somewhere along a biological continuum. This is a fact which is often forgotten by some who work within narrower spheres.

The book is recommended to all readers —professional and lay, alike—for its comprehensiveness, simplicity and thoughtfulness.

Gerald D. Klee